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Female	114.7	116.4	117.7	118.7	120.4	123.6	127.1	129.8	132.5	133.7	135.4
DIASTOLIC **Male	76.4	78.1	78.8	79.5	80.4	81.4	82.3	83.3	84.3	84.5	84.0
Female	75.8	77.1	78.0	78.6	79.9	81.9	83.9	85.4	86.8	86.8	84.4

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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

APRIL, 1954

ORIGINAL ARTICLES

INTRAVENOUS CHOLECYSTOGRAPHY AND CHOLANGIOGRAPHY: REPORT OF PRELIMINARY OBSERVATIONS

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The need for a reliable non-surgical method of roentgenologically visualizing the major extrahepatic bile ducts has long been evident. This need was partially met with the introduction of the newer cholecystographic media, iodoalphionic acid (Priodax), iodopanoic acid (Telepaque), and triiodoethionic acid (Teridax). In patients whose gallbladders are opacified by these orally administered contrast media, serial exposures made in the phase of gallbladder contraction following oral ingestion of fat often succeed in demonstrating variable portions of the cystic and common bile ducts. The ducts are not visualized, however, in many of the patients studied in this fashion[8]. In an exceptional patient with a non-functioning gallbladder or whose gallbladder has been removed, especially if there is some disturbance interfering with the free flow of bile into the duodenum, the ducts may be visualized after the oral ingestion of these media. In general, however, they are unreliable for such purposes because of their unpredictable rate of absorption from the gastrointestinal tract and their failure ordinarily to attain adequate concentration in the extrahepatic ducts.

There has recently been developed an intravenously administered contrast medium* which opacifies the extrahepatic bile ducts even when the

*Temporarily designated Be-426 but soon to be named Cholografin (E. R. Squibb and Sons) and identical with Biligrafin (Schering, A. G.), which has been investigated in Germany under the designation SH-216. This material was kindly supplied by Dr. Mark H. Lund, Assistant Medical Director, The Squibb Institute for Medical Research.

gallbladder is diseased or has been removed. Considerable attention is being given to this medium abroad, particularly in Germany[1,2,3,4,5,6], but no report has yet appeared by American investigators.

We have been engaged in a systematic study of this contrast medium since June, 1953. While much remains to be learned before the material can be properly evaluated, we are sufficiently encouraged by our observations thus far to feel that it represents a decided advance in this field. We believe, therefore, that a report of our preliminary studies is warranted at this time to direct attention to the material and to afford a background to guide others who may be attracted to investigate its use.

Material. Present knowledge regarding the chemical composition and properties of Be-426 is based on data reported by the investigators who have had the opportunity to use this material and supplemental information supplied by the research division of the manufacturer[1,2,3,4,5,6,9]. These data indicate that Be-426 contains essentially the di-sodium salt of N,N′ adipyl-bis(3-amino-2:4:6 triiodobenzoic acid). This substance is a crystalline powder which readily dissolves in water to yield a colorless solution. It has a molecular weight of 1183.35 and an iodine content of 64.32%.

When the drug is given intravenously, it is rapidly carried to the liver where approximately 90% is actively excreted by the liver cells, traces appearing in the bile after only several minutes[1]. The concentration of the drug in the bile is considerably greater than that in the blood, resulting in opacification of the larger bile ducts and subsequently the gallbladder. Eventually, the drug reaches the intestinal tract with the bile and is finally eliminated in the feces. Only about 10% or less of the intravenously administered material is excreted by the kidneys[1]. In the event liver function is impaired, however, a much larger proportion is excreted in the urine. Depending on the concentration of Be-426 in the urine, an excretory urogram may be produced.

The toxicity of Be-426 is reputed to be comparatively low[1,9]. The LD50 intravenous dose for rats has been reported to be 3.4 gm. per kg. of body weight[1]. Rabbits tested for pyrogenicity of the material have not shown significant rises in temperature[9].

Method of Study. In the 6-month period from June through December, 1953, 33 studies were conducted on 30 subjects. This group was composed of 6 males ranging in age from 24 to 68 years and 24 females ranging in age from 29 to 75 years. Nine had intact gallbladders and 21 had undergone cholecystectomy. Of the 9 whose gallbladders were intact, 3 were entirely asymptomatic and were considered to represent normal subjects; 6 presented gastrointestinal symptoms, but in only 5 of these were the symptoms clinically suspected as probably due to biliary tract disease. Of those whose gallbladders had been removed, only one was asymptomatic, but was known to have had a residual common duct stone 2 years prior to this study, when she was last examined by cholangiography obtained by introducing contrast material through an indwelling T-tube. While the remaining 20 patients presented symptoms referable to the upper abdomen, in only 4 of them was it clinically suspected that the symptoms had their origin in residual biliary tract disease and in another 4 this possibility was clinically entertained but seemed less likely.

In 24 of the 30 subjects, a preliminary hepatic function profile was obtained, usually 24 hours before Roentgen examination. The tests comprising this profile included: quantitative determination of 1-minute direct-reacting and total serum bilirubin, cephalin cholesterol, colloidal gold and colloidal red flocculations, thymol turbidity, 18-hour turbidity ratio, zinc sulfate (gamma globulin) turbidity, serum alkaline phosphatase, total

serum cholesterol and cholesterol esters, serum phospholipids, fatty acids, neutral fat and total lipids, and bromsulfalein retention.

A preliminary roentgenogram of the right upper abdomen was made in each subject, after the area was first localized fluoroscopically. While this film was being developed, a test dose of 1 cc. of Be-426 was given intravenously and the subject observed for approximately 10 minutes. If no untoward reaction developed, 40 to 60 cc. of the material was then slowly injected intravenously over 8 to 10 minutes. The total dose used initially was 40 cc., but this was increased to 60 cc. in the last 12 studies. Immediately following completion of the intravenous injection, a roentgenogram was made. Serial roentgenograms were then made every 10 minutes for 1 hour and again at 2 hours. In 17 subjects another roentgenogram was made at 3 hours, and in 9 at 4 hours also. If the gallbladder was intact and was visualized on earlier roentgenograms, an additional exposure was made at 2½ hours. In 3 subjects whose gallbladders were visualized and appeared to be free of obvious calculi, fat (Cholex) was given by mouth and roentgenograms were taken 10 and 20 minutes later.

In all cases a Potter-Bucky diaphram was used. The Roentgen factors were 300 milliamperes, 0.25 second exposure, and 60 to 90 kilovolts, depending on the thickness of the individual. The subjects were placed in a 15-degree right posterior oblique supine position. Depending on the situation disclosed by the roentgenograms on which the duct was first seen, the position of the subject was changed as necessary to displace the shadow of the common bile duct from that of the spine. A

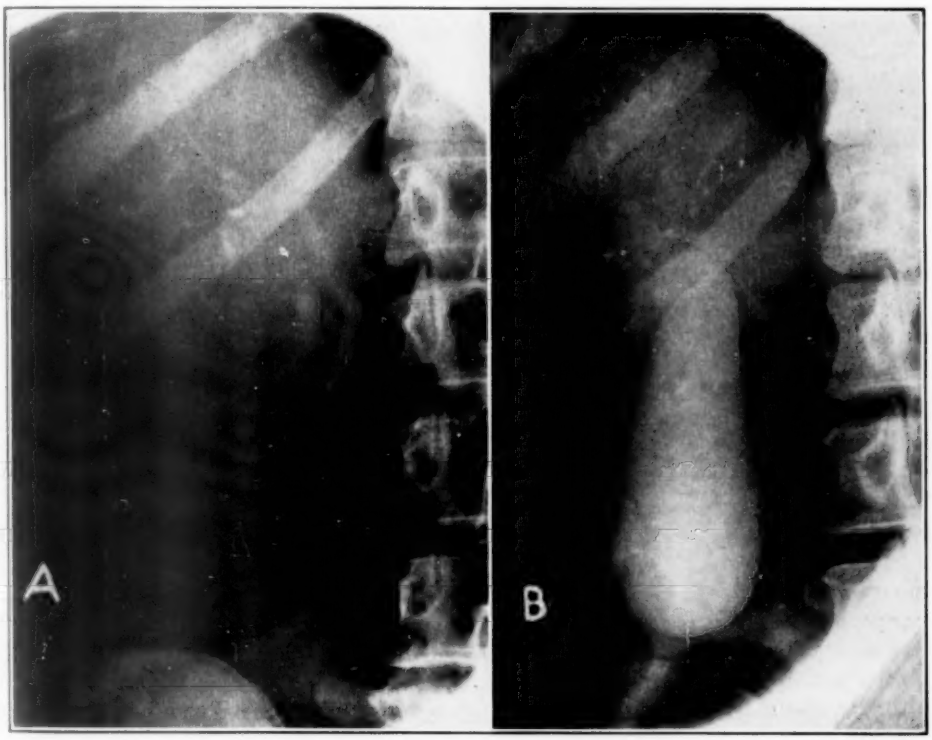

Fig. 1.—Roentgenograms taken 30 minutes (A) and 2 hours (B) after intravenous injection of 60 cc. of Be-426. The extrahepatic bile ducts are well visualized before the gallbladder is fully opacified. The quality of the cholecystogram and the clear evidence of multiple radiolucent calculi within the gallbladder are to be noted. No fat had been given prior to roentgenogram (B).

small cone was used to reduce stray radiation. The focal film distance in each case was 46 inches. All exposures were made on 8 inch by 10 inch films.

Results. SUBJECTS WITH INTACT GALLBLADDERS. The gallbladder was visualized in 7 of the 9 subjects whose gallbladders were intact. One of the 2 whose gallbladders failed to visualize was jaundiced and was subsequently determined to have metastatic carcinoma. The ducts were well demonstrated in the other, indicating that failure of the gallbladder to opacify in this case was due, in part at least, to cystic duct obstruction.

Abnormal findings were obtained in 4 of the 5 patients with intact gallbladders whose symptoms were clinically suspected as probably being due to biliary tract disease. The gallbladder failed to visualize in 2 as noted above and in 2 others radiolucent calculi were demonstrated (Fig. 1).

In 6 of the 9 subjects in this group the common duct was visualized. The duct was not visualized in the jaundiced patient with metastatic carcinoma whose gallbladder also failed to opacify. The other 2 subjects whose ducts were not seen had no signs or symptoms of biliary tract disease; their gallbladders were well shown and no reason was apparent for failure to visualize the ducts.

SUBJECTS WHOSE GALLBLADDERS WERE PREVIOUSLY REMOVED. The common duct was successfully visualized in 19 of these 21 subjects.

Of the 2 whose ducts were not seen, one was among the first patients studied and no simultaneous determination was made of liver function. Her gallbladder had been removed 6 years before. Frequently recurring attacks of severe epigastric pain began about 2 years after operation. A total dose of 40 cc. of Be-426 was given. On the roentgenograms obtained at 10 and 20 minutes after injection of the material a faint partial renal pyelogram could be seen.

The second failure occurred in a very obese female who had undergone choledocholithotomy 2 years previously and was found, on postoperative cholangiography carried out through an indwelling T-tube, still to have at least 1 common duct stone. Despite this, she had been entirely asymptomatic since operation. At the time intravenous cholangiography was performed, hepatic function studies revealed a total serum cholesterol of 310 mg. per 100 cc. and bromsulfalein retention of 8% at 30 minutes (2 mg. per kg. dose). No urogram was obtained and opaque material was not present in the bowel.

Other than for variable degrees of dilatation, no abnormalities were observed in the common hepatic and common bile ducts of the 19 subjects in this series whose ducts were visualized. The exact position of the junction of the common hepatic and common bile ducts could not be reliably determined in many subjects without gallbladders. For this reason, we approached the problem of change in size of the major terminal ducts by estimating the greatest width on the roentgenograms, regardless of whether this occurred in what was obviously common bile duct or may have been common hepatic duct, and have referred to these measurements as those of the "common duct." When the maximal width of the common duct so defined was measured on the roentgenograms of a normal subject studied in the same fashion and prior to evacuation of the gallbladder, the duct measured 8 mm. This value coincides with the upper limit of normal for the maximal diameter of the common duct as measured on roentgenograms obtained during peritoneoscopic cholangiography[7]. Similar measurements made on the roentgenograms

of the 19 cholecystectomized individuals with visualized common ducts gave values ranging from 4 to 13 mm. (Figs. 2 and 3). Of these, 11 had ducts measuring 8 mm. or less. Of the 8 patients clinically suspected of having symptoms arising from residual biliary tract disease, the common duct failed to visualize in one, showed a maximal width of 8 mm. or less in 5, and a maximal width greater than 8 mm. in only 2.

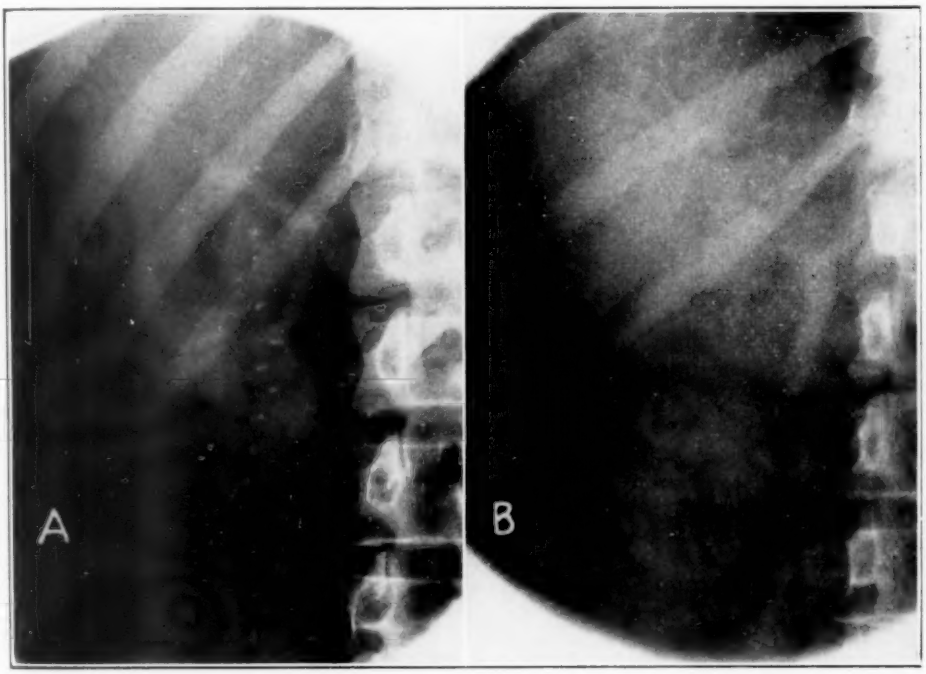

Fig. 2.—Roentgenograms in 2 cholecystectomized patients showing variation in size of the common duct. Both patients had symptoms referable to the upper abdomen but these were not clinically considered to be due to residual biliary tract disease. (A) 40 minutes after 60 cc. of Be-426. (B) 10 minutes after 60 cc. of Be-426.

INTERVAL FROM INJECTION TO VISUALIZATION. The common duct could be detected in most cases in the roentgenogram made 10 minutes after the intravenous injection of Be-426, and in nearly all cases in the 20-minute film. In addition to the common duct, portions of the intrahepatic biliary ducts, both hepatic ducts and the common hepatic duct were frequently seen in the 10- and 20-minute films. Maximal intensity of the common duct was usually achieved from 20 to 40 minutes after injection.

In patients with gallbladders the ducts were visualized in the same time interval and in the same fashion as in cholecystectomized individuals (Fig. 1). Opacification of the gallbladder was usually first apparent in from 40 to 60 minutes after injection, and maximal intensity was usually reached in 2 to 2½ hours.

When the ducts were visualized, they remained detectable for at least 1 hour after injection; in most cases opacifica-

tion persisted for 2 hours and occasionally for as long as 4 hours.

QUALITY AND DEGREE OF VISUALIZATION. The quality of the cholecystograms obtained after the intravenous administration of Be-426 was at least equal to that after the newer orally ingested contrast media. In 2 of our cases radiolucent calculi were clearly shown (Fig. 1). We observed no lay-

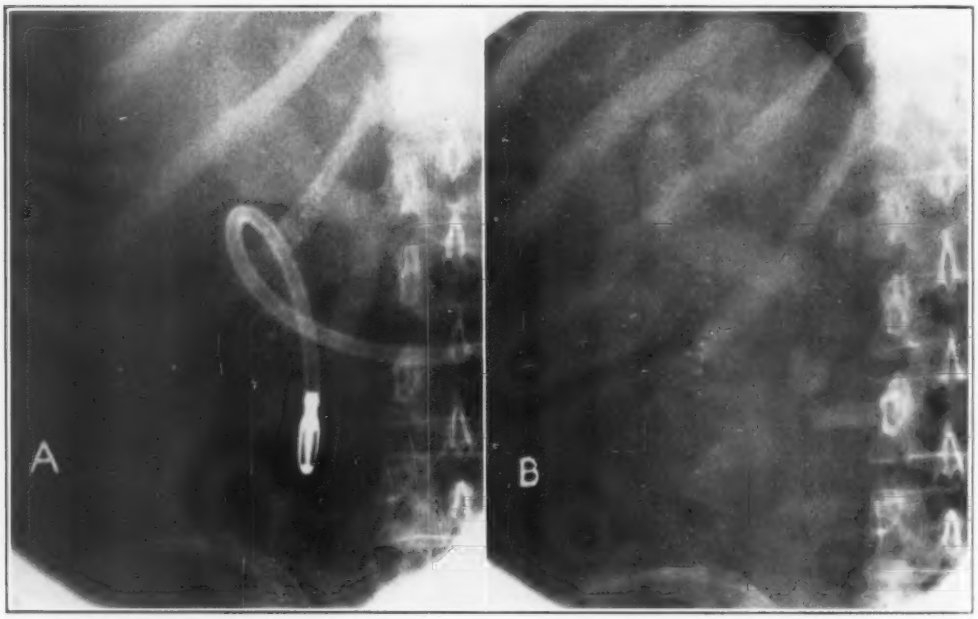

Fig. 3.—Roentgenograms in a cholecystectomized patient studied on two different occasions. (A) 40 minutes after 60 cc. of Be-426 and 20 minutes after start of continuous intraduodenal drip of 0.1 N HCl; (B) 40 minutes after 60 cc. of Be-426 and 20 minutes after subcutaneous injection of 10 mg. of morphine sulfate. Films taken prior to the administration of these agents showed a dilated common duct, but this was not as wide as after HCl and morphine.

ering of the contrast material within the gallbladder in roentgenograms made with the subject upright or in right lateral decubitus positions. This phenomenon has been reported by others[6] and has been attributed to the rapid entry of bile containing contrast material of high specific gravity. Prompt evacuation of the gallbladder occurred after oral ingestion of fat.

Opacification of the ducts in cholecystectomized individuals was sometimes disappointingly faint, especially in obese persons. The degree of opacification was roughly divided into 2 categories: (1) "faint," by which was meant density sufficient to outline the ducts but insufficient to permit diagnosis or exclusion of radiolucent calculi; (2) "adequate," by which was meant density which we regarded as sufficient not only to recognize ductal outline but also to permit the detection of radiolucent calculi with at least reasonable certainty. Using such criteria, the degree of ductal opacification in the 19 cholecystectomized subjects whose ducts were visualized was classified as faint in 7 and adequate in 12. It was our impression that whereas a dose of

40 cc. of Be-426 often provided adequate visualization, the use of 60 cc. resulted in improved opacification. In those with functioning gallbladders, of course, visualization of the ducts may also be obtained with even better contrast during gallbladder contraction after oral ingestion of fat.

The terminal end of the common duct was poorly seen and most often was not seen at all, even though serial roentgenograms were made at intervals of 10 minutes. Opaque material was noted in the second portion of the duodenum at some time during the period of observation in 8 of our 33 studies. While this was helpful in locating the termination of the common duct, the intraduodenal contrast material sometimes tended to obscure this portion of the duct (Fig. 2 [A]).

With the aim of improving the degree of opacification of the ducts and perhaps also of bringing the important terminal end into better view, the effect of certain pharmacologic agents was tested. Morphine sulfate (10 mg.) was given subcutaneously to 7 subjects immediately after the 20-minute roentgenogram. Clinically experienced pain was reproduced in 2 of these subjects. In only 1 of the 7, however, did the common duct become wider and more opaque (Fig. 3 [B]); in none was there better visualization of the terminal end of the duct. The failure of morphine consistently to increase the density of the common duct was disappointing. Failure to visualize the terminal end of the duct any better was rather expected, however, since the spasmogenic action of morphine is exerted not only on the musculature of the choledochal sphincter, but on that of the adjacent duodenum as well.

In 1 subject a Rehfuss tube was introduced into the stomach and then placed under fluoroscopic control so that its tip was in the descending limb of the duodenum. Immediately after the 20-minute roentgenogram, constant intraduodenal drip of 0.1 N HCl was started and serial exposures were made in the usual manner. The common duct showed increased filling and dilatation but its distal portion was not seen any better (Fig. 3 [A]).

Two subjects were given inhalations of amyl nitrite and glyceryl trinitrate (0.4 mg.) sublingually after the 20-minute roentgenogram. In neither case was the terminal common duct visualized in subsequent roentgenograms. Two other patients were given nitrites in similar fashion, within 5 minutes after the subcutaneous injection of morphine sulfate. Pain, which had developed in these 2 patients very shortly after the administration of morphine, was promptly relieved by the nitrites but no appreciable change occurred in the appearance of the common duct. In still another individual, nitrites were administered as described, 20 minutes after the cessation (corresponding to 55 minutes after the start) of constant intraduodenal drip of HCl. In this case too there was no apparent change in the appearance of the duct.

Accumulations of gas in the colon frequently presented a problem. No special effort was made to prepare the colon before Roentgen examination in most of these studies. In the later ones, however, 60 cc. of castor oil was given from 15 to 20 hours before examination. Use of the latter seemed helpful but did not solve the problem.

CORRELATION WITH LIVER FUNCTION. Three patients in this series either had hepatobiliary disease in the recent past, were jaundiced, or showed some derangement in hepatic function at the time intravenous cholecystography and cholangiography were attempted. In all 3 there was either faint or no visualization of the gallbladder or ducts. There was no opacification of either

the gallbladder or ducts in one patient who was jaundiced as a result of metastatic carcinoma. The ducts failed to visualize in a second patient who had previously undergone cholecystectomy and choledocholithotomy and whose bromsulfalein retention was 8% at 30 minutes (2 mg. per kg. dose). The third patient showed only very faint visualization of the common hepatic and upper common bile ducts in the roentgenograms obtained from 20 through 60 minutes after injection of Be-426. Just prior to the Roentgen study, total serum cholesterol was recorded as 321 mg. per 100 cc., cephalin cholesterol flocculation was 3 plus at 24 hours and there was bromsulfalein retention of 16% at 30 minutes (2 mg. per kg. dose). In still a fourth patient with chronic relapsing pancreatitis who had been jaundiced during an acute relapse that occurred just before intravenous cholecystography was carried out, and whose 1-minute direct-reacting serum bilirubin measured 0.52 mg. per 100 cc. at the time of Roentgen study, the gallbladder and common duct were adequately visualized.

VISUALIZATION OF THE KIDNEYS. Incomplete visualization of the renal pelvis and calyces was frequently obtained after the intravenous administration of Be-426. The time from injection to initial appearance of opaque material was in general the same for the kidneys as for the bile ducts (Fig. 1 [A]). Pronounced excretory urograms were obtained in 2 patients whose ducts did not visualize. On the other hand, portions of the kidneys were seen in 7 of the 19 cholecystectomized individuals whose ducts were opacified, in one subject whose gallbladder visualized but whose ducts were not seen, and in 4 of the 5 persons showing opacification of both the gallbladder and ducts.

REACTIONS. No untoward reaction developed within the observation period after the test dose of 1 cc. of Be-426. Minor reactions developed in 3 individuals immediately after intravenous injection of the full dose. Two subjects began to perspire and complained of a burning sensation in the eyes, nose or face. A third developed itching erythematous patches on the face and also perspired. In all 3 the reactions were mild in degree and completely subsided within 10 minutes without treatment.

There was no evidence in any subject of phlebitis or local irritation at the site of injection of the material. Extravascular injection in one person caused nothing more than local pain.

Discussion. The ability to perform combined cholecystography and cholangiography within a period of approximately 3 hours represents a distinct advance in the field of diagnostic roentgenology. Of even greater import is the availability of a non-surgical means of opacifying the extrahepatic ducts with gratifying regularity. Through the use of this medium the way is now open to detect alterations in the bile ducts, even in persons without gallbladders. Information of physiologic importance may be gathered with respect to the mechanism of gallbladder and bile duct filling and emptying, changes in the ducts subsequent to cholecystectomy, and the influence on the gallbladder and bile ducts of emotional stresses, certain bodily states and various pharmacologic agents.

Despite the distinct advantages possessed by Be-426, the present use of the preparation is not without deficiencies. Although we have not as yet encountered any serious reactions, it may be anticipated that the intravenous introduction of a compound of such high iodine content will produce

untoward reactions in some persons, especially in those who may be sensitive to iodine. The degree of opacification, while entirely adequate for diagnostic purposes in most instances, is not as intense as might be desired. The terminal portion of the common duct, so often an area of crucial importance from the standpoint of lodgement of calculi and disorders affecting the duct, is poorly seen with existing techniques. The compound cannot be relied upon to visualize the ducts in jaundiced patients, and it is in just such individuals that information regarding the common duct is most desired. The excretion of the preparation from the liver into the bile is largely governed by the functional integrity of the liver. In patients with biliary and pancreatic disease impairment in hepatic function is commonplace. The possibility seems great, therefore, that faint or no visualization of the gallbladder and ducts may occur distressingly often in the patients we are most interested in studying by this method. Indeed, the ability of intravenously administered Be-426 to pass through the liver and into the bile in good concentration may in itself constitute a test of hepatic function which may or may not prove correlative with the usual function tests[1].

The diagnostic potentiality of this method of examination is clearly evident. It may be anticipated that some gallbladders which fail to become visible after orally administered contrast media will be opacified after Be-426 is given intravenously. Indeed, such occurrences have already been observed[2,3,6]. The explanation rests on the fact that when oral contrast media have been given, opacification of the gallbladder basically depends on the ability of the gallbladder to concentrate the material. After intravenous administration of Be-426, however, contrast medium in high concentration appears in the bile within a short time. Sufficient material may enter the gallbladder to cast a shadow without the need for additional concentration within this viscus.

It has been suggested that intravenous cholecystography and cholangiography using Be-426 may serve to distinguish primary disease of the gallbladder with impairment in concentrating power from cystic duct obstruction, both of which would be expected to result in non-visualization of the gallbladder when oral contrast media are given[3]. If the gallbladder becomes visible within the expected period after injection of Be-426, but does not become more opaque while the ducts opacify in normal fashion, it may be assumed that the cystic duct is patent but that the concentrating function of the gallbladder is impaired. Should the ducts visualize as normally expected, but the gallbladder show only a faint shadow early in the study and not achieve normal density until much later on, the presence of partial cystic duct obstruction interfering with free inflow of contrast-laden bile into the gallbladder may be suspected. If the ducts become normally opaque, but the gallbladder never becomes visible, it may be assumed that there is some obstruction of the cystic duct with which intrinsic disease of the gallbladder may or may not be associated.

Common duct stones were not detected in any of the individuals on whom this report is based. This is in part due to the selection of subjects. We sought to initiate our studies on subjects without symptoms pointing to the biliary ducts, in order to secure a base line against which to compare the findings in those with such symptoms. As a consequence, patients who might be expected to have common duct stones comprised only a small

part of the group studied by us. In one cholecystectomized patient with recurring biliary colic intensively studied by one of us (J.E.B.), however, 2 subsequently proved stones were clearly demonstrated in the distal common duct after Be-426 administered elsewhere.*

The size of the common duct before and after removal of the gallbladder is of interest clinically and physiologically. From the purely technical aspect, *apparent* variations in size may result from differences in thickness of the patient and change in focal distance. Tonus of the duct and of the choledochal sphincter, the degree of filling of the duct and the pressures exerted at the time by liver secretion and gallbladder contraction are among the factors capable of altering the *actual* size of the duct. Despite these variables, study of the ducts after intravenous injection of Be-426 would seem to provide the best means yet available to study the common duct under natural circumstances. The limited number of observations we have been able to make to date would suggest that the size of the duct after removal of the gallbladder is variable and is not directly correlative with the presence or absence of symptoms clinically considered to arise from residual disease of this structure.

Considerable physiologic interest attaches to the manner in which the gallbladder fills and empties. Our observations on the course of events following intravenous administration of Be-426 are in accord with those of others[1,2,3,5,6] and lend support to existing thought regarding the physiologic mechanisms involved. When the bile ducts are visualized, they do so before the gallbladder. This suggests that bile entering the extrahepatic ductal system promptly descends at least to the area of the choledochal sphincter and some probably passes into the duodenum. It would seem that as resistance to flow occurs at the sphincter and as pressure rises within the common duct, bile is forced through the cystic duct into the gallbladder. Some filling of the gallbladder may also result from simple deflection of on-passing bile.

The surprisingly long persistence of opaque material within the common duct is an interesting phenomenon, the explanation for which is not altogether clear to us at present. It is possible that persisting opacification of the bile ducts is in the main a reflection of the time required for the blood to be cleared of its content of contrast material. The latter can be expected to continue to appear in the bile as long as any of it remains in the blood. Repeated entry of contrast material into the ducts could also ensue as a result of enterohepatic circulation, although this phenomenon has been alleged not to occur with Be-426[9]. Other possible contributing factors which suggest themselves are concentration within the bile ducts and resistance to flow offered by the choledochal sphincter. In cholecystectomized persons and in patients with diseased gallbladders or cystic duct obstruction, the extrahepatic bile ducts might be expected to retain a larger amount of contrast material for longer periods of time[3].

It seems clear from these considerations that intravenous cholecystography and cholangiography as now permitted through the use of such a medium as Be-426 provides a new avenue of approach in clinical medicine that should prove diagnostically useful. Its potential value as a tool for the study of physiologic mechanisms affecting the gallbladder and bile ducts is also of great promise.

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Summary and Conclusions. 1. Preliminary observations are reported on rapidly obtained cholecystography and cholangiography, using a new intravenously injected medium currently designated Be-426.

2. The bile ducts are visualized before the gallbladder becomes opaque and may be detected 10 minutes after intravenous injection of the medium.

3. Visualization of the gallbladder is of a quality comparable to that obtained after the newer orally administered cholecystographic media. Radiolucent calculi are readily detected and clearly shown.

4. The common duct and portions of the other major extrahepatic bile ducts may be visualized with a high degree of regularity in patients whose gallbladders have been removed.

5. Impairment in hepatic function interferes with the secretion of Be-426 into the bile and may result in faint or no visualization of the gallbladder and ducts.

6. The degree of opacification of the bile ducts is many times faint and the terminal end of the common duct is often poorly seen.

7. No serious systemic or local reactions were observed in the group of subjects studied.

8. Intravenous cholecystograpy and cholangiography may provide a valuable tool for the study of physiologic mechanisms affecting the gallbladder and bile ducts.

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POST-CHOLECYSTECTOMY ORAL CHOLANGIOGRAPHY* A PRELIMINARY REPORT

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This report of 31 patients investigated by oral cholangiography is, to the best of our knowledge, the first in the literature. Of 18 who had biliary tract symptoms following cholecystectomy, 15 showed a visualization of the bile ducts. Of 7 comparable postcholecystectomy patients without symptoms, 6 visualized the bile ducts. Of 4 patients without symptoms who had a subsequent choledochoduodenostomy, none visualized the bile ducts. In addition, the results of oral cholangiography are given in 2 patients having a nonfunctioning gallbladder or "physiologic cholecystectomy."

There have been few improvements in cholecystography since its introduction[7,8,17]. Chief among these has been the use of radiopaque compounds of higher iodine concentration giving a more intense gallbladder shadow[3,13,16,22]. With these compounds, the bile ducts occasionally are visualized following the contraction of the gallbladder in response to a fat meal[16]. Following cholecystectomy, routine cholecystograms have occasionally shown remnants of the cystic duct[21].

All other procedures for visualizing the bile ducts have involved surgical procedures. These usually have been the introduction of dye into the common duct by needle, "T" tube or catheter[2,11]. The bile ducts also have been visualized by the use of a peritoneoscope, introducing dye into the gallbladder by a needle[12,14,15].

An intravenous dye (Biligrafin) also has been used for visualization of the extrahepatic bile ducts, both with a functioning gallbladder and after cholecystectomy[13a].

In the absence of the concentrating function of the gallbladder or bile fistula, oral cholangiography affords to date the only non-surgical method of visualizing the bile ducts. The obvious advantages of an oral procedure include the elimination of the inconvenience, expense and risk involved in any surgical procedure.

The types of conditions investigated to date by oral cholangiography are as follows:

HYPERTONIC BILIARY DYSKINESIA. Colp[5] states: "The most common cause of the post-cholecystectomy syndrome is dyskinesia of the sphincter mechanism, with which there may be associated calculi, retained cystic duct, common duct stricture, cholangitis or pancreatitis." The presence of biliary dyskinesia with the post-cholecystectomy

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syndrome has been reported by many investigators[4,9,19].

DYSKINESIA WITH INCISIONAL HERNIA. In one of the patients reported in our series, an incisional hernia was the apparent etiologic factor in producing biliary colic. Other than Beye's[1] report, this important subject has received little attention in the literature.

CHRONIC PANCREATITIS. The frequency with which pancreatitis is associated with biliary tract disease is well known[18]. That chronic pancreatitis may be associated with the post-cholecystectomy syndrome is an established fact[4,5,9,19,20].

CYSTIC DUCT REMNANT AND "RE-FORMED GALLBLADDER." Inadequate surgery at the time of cholecystectomy may result in a retained cystic duct remnant or a "re-formed gallbladder"[1,4,9,10]. This term is used because there is evidence that the gallbladder found at re-operation after cholecystectomy is not merely a dilated pouch but, on microscopic examination, shows actual regeneration of the gallbladder wall[1,10]. A case reported in this series tends to confirm this fact. The clinical importance of recognizing these lesions lies in the fact that they are usually the seat of inflammation, frequently associated with the presence of stones.

"PHYSIOLOGIC CHOLECYSTECTOMY." On cholecystographic examination, the common finding of non-visualization of the gallbladder indicates, in most cases, the presence of a non-functioning gallbladder due to a cystic duct obstruction by a cholesterol stone. On the other hand, a small percentage of patients with the same roentgenologic finding may reveal, at operation, a normal gallbladder. Under these circumstances cholecystectomy may result in an aggravation rather than relief of preoperative symptoms[5,19,20].

With a non-visualized gallbladder, oral cholangiography affords a means of visualizing the common bile duct, giving evidence which should be of value in the differential diagnosis between functional disorders and organic disease.

Technique.† The patient is instructed to take 6 tablets of a 3-molecule iodine preparation* at intervals of 5 minutes, beginning at 6:00 p.m. After the last tablet, one teaspoonful of paregoric is given. The total amount of water taken is not to exceed one-half glass.

At 11:00 p.m., the above procedure is repeated.

At 8:00 a.m., one teaspoonful of paregoric is given with a swallow of water, otherwise no water is to be taken at any time until the completion of the test.

At 10:00 a.m., postero-anterior and oblique films are taken, localized to the right upper quadrant, using the shortest time exposure possible. The distance from the tube to the film is 36 inches.

If the bile ducts are visualized, an inhalation of amyl nitrite is given with the patient in the recumbent position. Further films are taken at intervals of 15 and 30 minutes. If there is no emptying of the bile ducts, a fat meal is given and another film taken in 30 minutes.

INTERPRETATION. The interpretation of the films is based upon the degree of visualization, the diameter of the common bile duct and the response to amyl nitrite, or the fatty meal, or both. The degree of visualization is noted as none, faint, fair or good. The uppermost limits of the average post-cholecystectomy bile duct shadow is provisionally considered to be approximately 6 mm. Diameters from 7 to 10 mm. are considered slight dilatation, those of 11 to 20 mm. moderate dilatation, over 20 mm. marked dilatation. The lack of response to amyl nitrite or the fat meal is presumptive evidence of organic obstruction of the ampulla of Vater or the common duct sphincter.

Case Reports. The following cases illustrate the findings in oral cholangiography.

BILIARY DYSKINESIA OF UNDETERMINED ORIGIN. CASE 1. L.B., a female, aged 58

†At present, we are investigating the results of giving the series of dye tablets at 11 p. m. and 7 a. m., followed by films taken at 12 noon.

*Telepaque was used in most of these cases.

years (courtesy of Dr. David Speer), was admitted with a 10-year history of epigastric fullness, belching, distention, intolerance to fats and roughage and a weight loss of 10 pounds. The discomfort was relieved by induced vomiting. There was no history of colic or jaundice. A cholecystotomy had been performed 24 years ago for cholelithiasis. This was followed by a cholecystectomy 17 years ago.

Laboratory findings included normal serum bilirubin, alkaline phosphatase and liver function tests. The duodenal drainage showed no concentrated bile; microscopic examination of the bile sediment was negative.

Oral cholangiogram showed a markedly-dilated common bile duct, two to three times normal size, without evidence of stones (Fig. 1A).

At operation, the bile duct was found to be dilated. There was no evidence of stones or lesion of the common duct sphincter, as shown by choledochotomy and duodenotomy.

The operative cholangiogram revealed findings similar to the oral cholangiogram, with free flow of dye into the duodenum (Figs. 1B and 1C).

CASE 2. D.D. was a female, aged 42 years, (courtesy of Dr. H. Doubilet) who following a cholecystectomy for cholelithiasis 20 years ago, had recurrent attacks of pain which led to reoperation 6 years ago. At that time, the bile duct was found to be markedly dilated to a diameter of 25 mm. with two stones in the common duct.

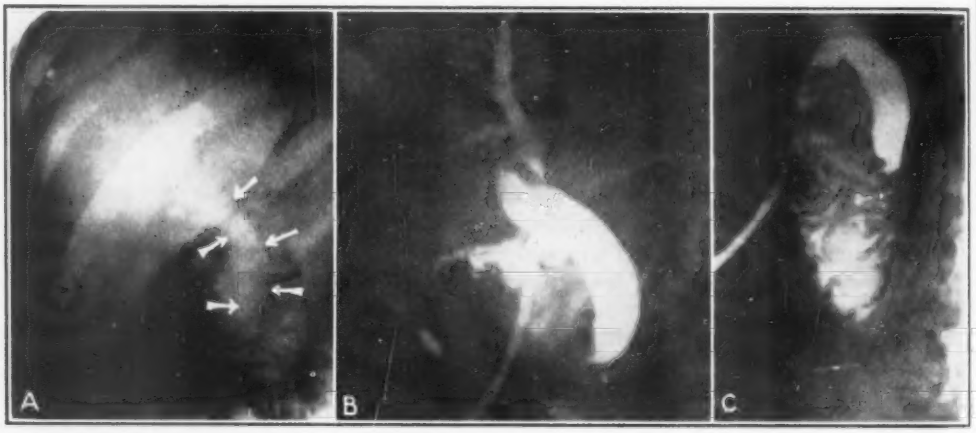

Fig. 1A.—Case No. 1. Illustrating a good concentration of dye in the common bile duct, which is markedly dilated.

Fig. 1B.—The operative cholangiogram, similar in appearance to that of the oral cholangiogram.

Fig. 1C.—Operative cholangiogram showing patency of the common duct sphincter, without obstruction. (Courtesy of Drs. David Speer and Sidney Weintraub.)

The patient was again seen in 1953 because of recurrent right upper quadrant pain with chills and fever. An oral cholangiogram showed a widely dilated common bile duct.

At operation, the common bile duct was found dilated, the sphincter greatly hypertrophied. There were no stones present. A sphincterotomy was performed with relief of symptoms.

CASE 3. Y.B. was a female, aged 60 years, who 5 years ago had suffered recurrent attacks of epigastric pain,

chills and fever. The cholecystogram at that time showed a normal visualization of the gallbladder, with multiple stones. On duodenal drainage, the bile was sterile. The serum bilirubin and liver function tests were normal. Three years ago, a cholecystectomy was performed for chronic cholecystitis and cholelithiasis. The gallbladder was covered with adhesions and filled with many stones. The common duct was normal.

When re-admitted in 1953, there was a history of three weeks' duration of recurrent dull aching right upper quadrant pain, acute for 4 days, with radiation to the left upper quadrant and right scapula. The oral cholangiogram showed a faint visualization of the common bile duct which was not dilated. The gastrointestinal series was negative. The clinical impression was that of a biliary dyskinesia.

CASE 4. H.G. was a male, aged 50 years, who complained of mild attacks of right upper quadrant pain following cholecystectomy, for a single stone, 2 years previously.

Oral cholangiogram revealed no visualization of the bile ducts.

Medical therapy, which consisted of the use of bland diet, reassurance, sedative and antispasmodics, resulted in the relief of symptoms.

CASE 5. B.C. was a female, aged 30 years. In 1953, this patient had cholecystectomy for cholelithiasis, one month previous to admission.

Oral cholangiogram showed no visualization of the bile ducts.

The patient has biliary colic similar to her preoperative symptoms, the clinical diagnosis was biliary dyskinesia.

CASE 6. G.B. was a female, aged 51 years. Five years before admission, this patient had a cholecystectomy for cholelithiasis. Severe attacks of epigastric pain occurred 6 months and 2 weeks before admission, the first requiring hospitalization elsewhere.

Oral cholangiogram revealed a faint visualization of a common bile duct which was not dilated. Following the second dose of paregoric, the patient developed an attack of colic similar to the previous two attacks.

DYSKINESIA OF APPARENT NEUROGENIC ORIGIN. CASE 7. M.S. was a female, aged 45 years, who has been under observation for 18 years, with recurrent symptoms of epigastric and right upper quadrant pain, belching, distention, nausea, heartburn and an intolerance for fats. Cholecystectomy and appendectomy had been performed 15 years ago with findings of an enlarged gallbladder, no stones and an acute purulent appendicitis.

Recurrent symptoms began one month after operation. Repeated gastrointestinal series, duodenal drainages and numerous other tests have given normal findings. Oral cholangiogram revealed a faint visualization of a moderately dilated bile duct which emptied promptly in response to amyl nitrite. A psychiatric consultation resulted in a diagnosis of anxiety hysteria with hypochondriasis.

DYSKINESIA WITH MIGRAINE AND PSYCHONEUROSIS. CASE 8. F.R., a female, aged 46 years, was admitted in 1933 for intermittent right upper quadrant pain of 10-months' duration. Cholecystogram revealed, at first, normal visualization and emptying, later, delay in concentration. There was an intermittent elevation in icterus index. Duodenal drainage cultures were sterile. Diagnosis was biliary dyskinesia with psychoneurosis.

Cholecystectomy 19 years ago gave findings of pericholecystitis with many adhesions. There were enlarged glands of the common duct. The common duct was explored and found negative. Bile cultures were sterile.

Since cholecystectomy, there have been occasional attacks of colic with pain in the right upper quadrant. There were associated symptoms of migraine, nausea, belching and distention.

Laboratory findings revealed an occasional elevation of the icterus index. Duodenal drainages showed achlorhydria, occasionally cultures showed *E. coli*. The gastrointestinal series was negative.

Oral cholangiogram showed faint visualization of extra- and intrahepatic bile ducts which were slightly dilated. There was slight evacuation after amyl nitrite.

The psychiatric diagnosis was psychoneurosis with migraine.

DYSKINESIA WITH CHOLANGITIS. CASE 9. M.C., a female, aged 80 years, has been under observation for 14 years. Indefinite initial symptoms were gas, distention, occasional pain and nausea. The cholecystogram showed a gallbladder with a partially calcified wall. The duodenal drainage showed *E. coli* in the sterile cultures of bile. A cholecystectomy was done 13 years ago, when the cystic duct was found occluded by an encysted calculus.

Fig. 2.—Case No. 9. A good visualization of a moderately dilated common duct in a patient with biliary dyskinesia and chronic cholangitis.

Since operation, the patient has had intermittent attacks of colicky pain, belching, nausea and vomiting with an intolerance for fats. Numerous duodenal drainages showed an intermittent gastric hyperacidity with, invar-

iably, *E. coli* in the duodenal bile. The serum bilirubin and all tests of liver function were normal.

The oral cholangiogram showed good visualization of a moderately dilated common duct (Fig. 2). There was no evidence of stones.

An effort is now being made to clear up the cholangitis by the use of antibiotics.

occurred preoperatively. Repeated gastrointestinal series were negative except for the presence of a small hiatus hernia. Repeated electrocardiograms, blood counts, and sedimentation rates were normal.

The oral cholangiogram revealed a faint visualization of a slightly dilated bile duct.

At operation in July, 1953, there was found an incisional hernia. The dia-

Fig. 3.—Case No. 10. Faint visualization of a slightly-dilated common bile duct, in a patient with biliary dyskinesia.

DYSKINESIA WITH INCISIONAL HERNIA. CASE 10. P.M. is a female, aged 59 years on whom, 4 years before admission, a cholecystectomy had been performed for recurrent attacks of colic. At operation, there was found an enlarged gallbladder containing a single stone.

Following cholecystectomy, there were repeated attacks of severe epigastric pain, radiating to the back, different in character from those which

phragmatic hiatus opening was wide. The common bile duct was found dilated with a hypertrophic common duct sphincter. The operative cholangiogram showed a dilated common duct without evidence of stones. An external sphincterotomy was performed[6].

Following operation, there have been no attacks of colic, except one of the previous type which occurred follow-

ing paregoric, given for a repeat oral cholangiogram.

DYSKINESIA WITH PROBABLE PANCREATITIS. CASE 11. S.R., a female, aged 72 years, had a cholecystectomy 2½ years ago for chronic cholecystitis without stones. At that time the liver was found to be "inflamed." Since cholecystectomy, there had been recurrent attacks of epigastric pain with colic, severe for 6 months preceding admission, requiring repeatedly hypodermics of narcotics.

Upon admission, the serum amylase was 3 mg. per 100 cc. The secretin test was negative. The serum bilirubin was 0.45 mg. per 100 cc., cephalin flocculation test 2+, blood cholesterol 215 mg. per 100 cc., cholesterol esters 135 mg. per 100 cc. The gastrointestinal series showed a calcification in the region of the pancreas with a hypertonic stomach and pylorospasm.

The oral cholangiogram showed a faint visualization of the bile ducts which were slightly dilated.

The diagnosis was a probable chronic pancreatitis with pylorospasm, hypertonic biliary dyskinesia and gastric hyperacidity.

CHOLANGITIS AND PROBABLE CHRONIC PANCREATITIS. CASE 12. F.LaM., a female, aged 47 years was admitted with a history of acute epigastric pain, radiating to the left upper quadrant of 4-days' duration. She had chronic recurrent diarrhea with an intolerance to sweets and fats, weakness and anemia. There was demonstrated a persistent achlorhydria with histamine. She was "afraid to eat."

At cholecystectomy 15 years ago, one stone was found in the gallbladder.

Gastrointestinal series was negative. Barium colon enema showed spastic colon. Blood serum bilirubin and alkaline phosphatase were normal. Serum amylase estimations were 3.6 mg. and 4.4 mg. per 100 cc. after secretin. Glucose tolerance test revealed a hyperinsulinism with sugar of 45 mg. per 100 cc. Duodenal drainage showed no free hydrochloric acid in gastric contents, and no concentrated bile; cultures showed *E. coli*.

A diagnosis was made of probable chronic pancreatitis of intermittent obstructive type, with chronic cholangitis and gastric achlorhydria.

Oral cholangiogram showed faint visualization of bile ducts, not dilated.

Following dietary management, with dilute hydrochloric acid and phenobarbital, the patient's symptoms subsided.

POST-CHOLECYSTECTOMY AND POST-SPHINCTEROTOMY. CASE 13. E.B., a female, aged 50 years, was admitted with a history of recurrent attacks of obstructive jaundice following cholecystectomy 4 years previously. No stones were found at operation. Two years before admission, a laparotomy with choledochotomy revealed a pancreatitis, with enlarged nodes around the common bile duct. Eight months before admission, a transduodenal sphincterotomy had been performed with "T" tube drainage. The "T" tube has remained *in situ*. Upon admission, the serum bilirubin and liver function tests were normal. The pancreatic function tests were normal.

The cholangiogram performed by injection of dye into the "T" tube showed the common bile duct not dilated, with no evidence of stones. There was a free flow of bile into the duodenum.

Oral cholangiography, with the "T" tube closed, showed no visualization of the bile ducts.

The present symptoms are attributed to a chronic pancreatitis and chronic hepatitis.

DYSKINESIA WITH SUSPECTED COMMON DUCT STONE. CASE 14. H.J.S., a male, aged 70 years, had typhoid fever 37 years ago, and a cholecystectomy for

cholelithiasis 25 years ago. There were recurrent attacks of right upper quadrant colic for 5 years previous to cholecystectomy. He did well for 21 years after operation.

The present illness of 3½-years' duration consisted of recurrent acute attacks of pain similar to those before cholecystectomy. The attacks were associated with vomiting, chills, fever and on one occasion difficulty in breathing. Hypodermics were required for relief of pain three or four times. The patient was smoking 4 cigars and 6 pipes daily.

Previous laboratory investigations showed no gallbladder shadow in two cholecystograms. The gastrointestinal series and intravenous urogram were negative. Duodenal drainage revealed no concentrated bile, and cultures showed *E. coli*. The urine was negative. Chemical blood examination revealed normal serum bilirubin, amylase, lipase, total proteins, albumin and globulin; normal cephalin flocculation, thymol turbidity and alkaline phosphatase.

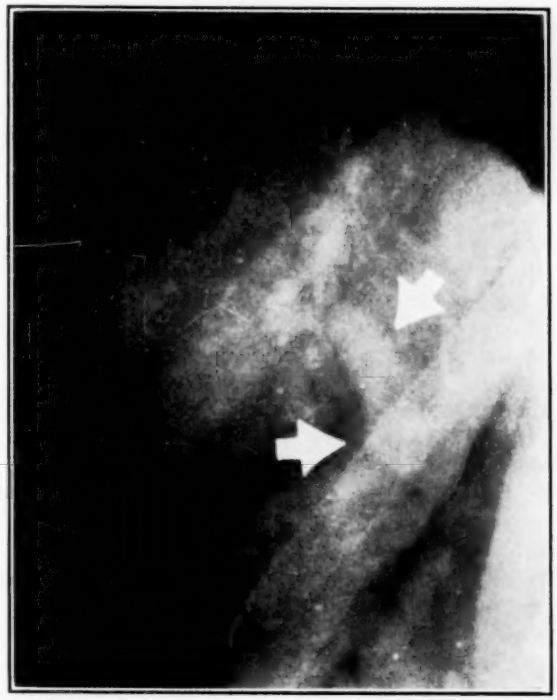

Fig. 4.—Case No. 15. Fair visualization of a moderately dilated common duct, showing a questionable defect of the lower end. A common duct stone was found at operation.

Physical examination revealed a severe degree of internal tension.

The oral cholangiogram showed a fair visualization of a moderately dilated common bile duct without evidence of cholelithiasis.

Laboratory tests were done 12 hours after a usual attack of biliary colic, precipitated by the ingestion of 3 drams of paregoric. Serum bilirubin at

that time was 2.8 mg., total serum protein 6.5 mg., serum albumin 3.5 mg., serum globulin 2.6 mg., alkaline phosphatase 5.1 units, serum amylase 1.8 mg., serum lipase 0.2 mg. and cholesterol 210 mg. per 100 cc.

The impression was that of a dyskinesia with a common duct stone. Exploratory laparotomy was advised.

PROVED COMMON DUCT STONE. CASE 15. A.C., a female, aged 52 years, had a history of cholecystectomy for cholelithiasis 2 years previously. No stones were found in the common duct at that time. Recently there had been recurrent attacks of colic, with right upper quadrant pain. There had been no jaundice, dark urine, or clay-colored stools.

The oral cholangiogram revealed a fair visualization of a moderately dilated common duct with a questionable filling defect in the lower end (Fig. 4).

A gallstone was found in the common duct at operation.

RETAINED CYSTIC DUCT REMNANT. CASE 16. H.G., a male, aged 64 years (courtesy of Dr. F. Howard Westcott) was admitted in March, 1953, with a history of having had an acute right upper quadrant pain with nausea and vomiting 4 months before admission. A cholecystogram revealed a pathologic gallbladder. A cholecystectomy done elsewhere revealed a single stone in the gallbladder; the common duct was said to be negative.

Three months before admission, one month after cholecystectomy, the patient developed a "different" type of right upper quadrant pain of a dull, aching character, which radiated to the right scapula and chest. This pain became progressively worse and was associated with nausea and vomiting for several days before admission.

Laboratory examinations gave these findings: Duodenal drainage showed no concentrated gallbladder bile. Microscopic examination of the bile sediment showed an occasional red blood cell. Normal values were obtained for the serum bilirubin, alkaline phosphatase, thymol turbidity and cephalin flocculation tests.

The gastrointestinal series showed a defect of the duodenum, suggesting the possibility of a carcinoma of the pancreas.

Oral cholangiography revealed a common bile duct of normal diameter with a retained duct remnant 3 to 5 cm. long with fair visualization.

The patient refused operation. He died shortly thereafter with a clinical diagnosis of a probable metastatic carcinoma of the brain.

CASE 17. M.P., a female, aged 63 years, was seen on March 4, 1953, with a history of epigastric pain which began in 1927, subsided after treatment and recurred from 1937 to 1940. A cholecystectomy was done in 1940; no stones were found. Following the operation, the pain gradually subsided. The pain recurred in 1947. Gastrointestinal series at that time and in 1940 were negative. In 1950, recurrent pains occurred. At that time the gastrointestinal series showed an esophageal ulcer. After 4-months' treatment the pain subsided.

The patient was admitted to the hospital in March, 1953, because of recurrent epigastric hunger pains. Gastrointestinal series then showed a peptic ulcer of the lower third of the esophagus, with a hiatus hernia. Fractional gastric analysis showed hyperacidity.

The oral cholangiogram showed a fair visualization of a moderately dilated common bile duct with a retained remnant of the cystic duct (Fig. 5).

Several months later, the patient developed lower abdominal pain with diarrhea. The barium colon enema showed, at the hepatic flexure, a cicatricial partial obstruction, due to a car-

Fig. 5.—Case No. 17. A fair visualization of the common bile ducts, the intrahepatic ducts and a retained cystic duct. The common bile is moderately dilated. This patient had a clinical diagnosis of biliary dyskinesia.

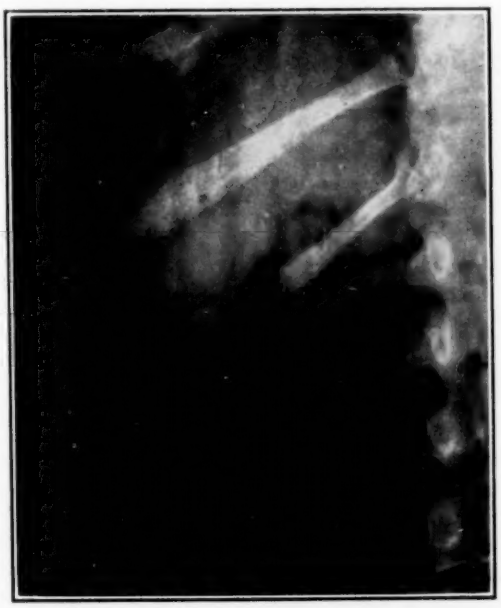

Fig. 6.—Case No. 18. A "re-formed gallbladder," as proved at operation, showing a gallbladder shadow similar to that of a normal cholecystogram.

cinoma. There were multiple diverticula. The intravenous pyelogram was negative.

At operation, there was found an annular carcinoma of the hepatic flexure of the colon. The entire right upper quadrant was a mass of adhesions, which obscured the biliary tract. The condition of the patient and the extensive nature of the colonic resection precluded investigation of the common bile duct.

"RE-FORMED GALLBLADDER." CASE 18. H.H. was a female, aged 41 years on whom a cholecystectomy had been performed 5 years before admission. Three days after the operation, the patient began to have recurrent attacks of right upper quadrant pain associated with nausea and vomiting. The attacks had persisted.

Upon admission, physical examination showed tenderness in the right upper quadrant.

The oral cholangiogram revealed a shadow of good concentration, about the size of an average gallbladder, in the right upper quadrant (Fig. 6).

At operation, there was found a "re-formed gallbladder" 2 by 4.5 cm. in size, similar in appearance to the usual gallbladder with chronic cholecystitis. The fundus was covered by a pad of fat in which there was embedded a cholesterol stone 5 mm. in diameter. The gallbladder was filled with a thick reddish bile in which there were 3 "mulberry" stones, each 8 mm. in diameter. The common duct was moderately dilated; the sphincter apparently normal.

An immediate cholangiogram revealed a shadow in the lower end of the common duct, from which a single stone was removed.

The pathologic examination of the "re-formed gallbladder" showed a smooth serosa with many adhesions. The mucosa was soft and velvety. The cystic duct was dilated. Microscopic examination showed evidence of chronic inflammation. The plical folds were flattened, the tunica propria and serosa were thickened and fibrotic. There was infiltration with lymphocytes and histiocytes, with calcific fragmentation and occasional giant cells. A few Aschoff-Rokitansky sinuses were seen.

PHYSIOLOGIC CHOLECYSTECTOMY. That additional information may be obtained by the oral cholangiographic technique in the patient with a roentgenologic diagnosis of a non-visualized gallbladder is illustrated by the following cases.

CHRONIC CALCULOUS CYSTIC DUCT OBSTRUCTION. CASE 19. L.A., a male, aged 54 years, who was seen by courtesy of Dr. Jere W. Lord, Jr., had a past history of good health. An attack of severe epigastric pain with shock had occurred 18 months before admission. At operation elsewhere, there was found an acute pancreatitis with two stones in the common duct. No operative procedure other than the laparotomy was performed. Recurrent attacks of colic began 3 months after operation. The last of these had persisted for 3 weeks with jaundice.

Upon his admission, the smooth liver edge was felt three fingers' breadth below the costal margin. The serum bilirubin was 1.27 mg. per 100 cc., the cephalin flocculation test was 2+. There were normal findings otherwise, relative to the alkaline phosphatase, bromsulphalein retention, serum pancreatic ferments and liver function tests.

The oral cholecystogram is shown in Fig. 7. The common bile duct was found to be moderately dilated with fair visualization. There was also a cluster of calcified stones, in the region of the gallbladder, with the configuration of a cystic duct.

At operation by Dr. Lord, the gallbladder was found to be diseased, its

cystic duct obstructed with small stones. The contents of the gallbladder were purulent in character. There were two stones, about 2 mm. in diameter, in the common bile duct. The liver and pancreas were normal in appearance. A cholecystectomy, choledocholithotomy and duodenotomy were performed without incident.

formed. The gallbladder was normal in appearance, contained no stones on palpation and was not removed. One year ago, the patient had an acute attack of colic. At that time, the cholecystogram was reported normal. Upon gastric analysis, the free hydrochloric acid was 101 units. A recurrent attack

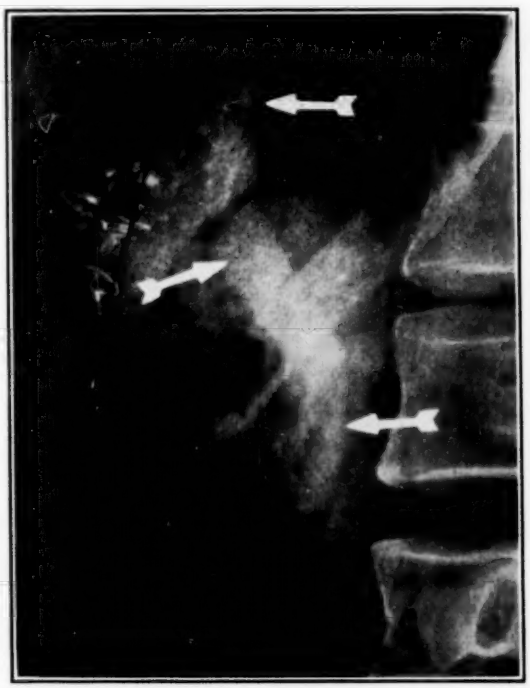

Fig. 7.—Case No. 19. A fair visualization of a moderately dilated bile duct, associated with a non-functioning gallbladder or "physiologic cholecystectomy" as proved at operation. There is a group of calcified stones seen above the top wire suture.

PHYSIOLOGIC CHOLECYSTECTOMY AFTER SPHINCTEROTOMY. That, following common duct sphincterotomy, oral cholangiography may not visualize the bile ducts in a patient with a "pathologic cholecystectomy" is shown by the following case.

CASE 20. A.B., a female, aged 41 years, had a pancreatitis 2 years ago for which a sphincterotomy was per-

of colic occurred 3 weeks before admission.

No visualization of the gallbladder was obtained with three cholecystographic examinations. The bile ducts were not visualized with an oral cholangiogram.

At operation, the cystic duct was found occluded by stones in the cystic duct. The common bile duct was not

dilated and contained no stones. The operative cholangiogram was normal, with a freely patent common duct ampulla. A cholecystectomy was performed.

PATIENTS HAVING NO POST-CHOLECYSTECTOMY SYMPTOMS. The following patients were considered to have no post-cholecystectomy symptoms referable to the biliary tract. In each case the oral cholangiogram showed no visualization of the bile ducts or a common bile duct which was not dilated or only slightly dilated.

CASE 21. I.K., a female, aged 70 years, had a cholecystectomy performed for chronic cholecystitis and cholelithiasis in October, 1953, at which time the common bile duct was found to be normal. In December the oral cholangiogram showed a faint visualization of the common bile duct, which was 7 mm. in diameter.

CASE 22. H.S., a female, aged 40 years, in May, 1953, had a cholecystectomy performed for cholelithiasis. In December the oral cholangiogram showed no visualization of the bile ducts.

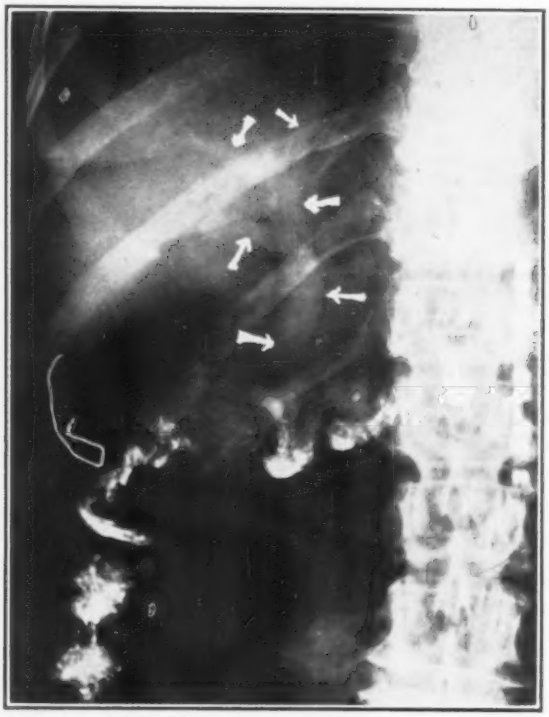

Fig. 8.—Case No. 26 A faint visualization of a slightly dilated bile duct in a patient with substernal pain due to coronary disease. There were no symptoms referable to the biliary tract.

CASE 23. A.R., a female, aged 47 years on whom, in 1952, a cholecystectomy and choledochotomy had been performed, for chronic cholecystitis and cholelithiasis. There were no stones in the common duct. In 1953 the oral cholangiogram showed faint visualization of the common duct, which was not dilated.

CASE 24. L.D., a female, aged 53 years, who in 1948, had a cholecystectomy for chronic cholecystitis. No stones were found at operation. In 1953 the oral cholangiogram showed a faint visualization of the common bile duct, 6 mm. in diameter.

CASE 25. O.P., a female, aged 70 years, who in 1948, had a cholecystectomy for cholelithiasis. In 1953, the oral cholangiogram showed good visualization of the common bile duct, 1 cm. in diameter.

CASE 26. H.U., a man of 61 years, on whom, in 1933, a diagnosis of gastric hyperacidity was made. In 1942 he had a cholecystectomy for cholelithiasis. For some years there had been recurrent attacks of substernal pain, associated with known coronary heart disease. In 1953 the oral cholangiogram showed faint visualization of a slightly dilated common bile duct (Fig. 8).

CASE 27. C.R., a female, aged 47 years, in January, 1953, had a cholecystectomy and choledochostomy for chronic cholecystitis, chronic cholangitis and cholelithiasis. Many cultures of duodenal bile had shown *E. coli*. At operation there was slight dilatation of the common bile duct. In December the oral cholangiogram showed a faint visualization of the common bile duct, which was not dilated.

CHOLECYSTECTOMY WITH SUBSEQUENT CHOLEDOCHODUODENOSTOMY. CASE 28. C.G., a female, aged 53 years, had a cholecystectomy for cholelithiasis in 1939. Because of recurrent colic a choledochoduodenostomy was done in 1949, at which time a papilloma was found in the lower end of the common bile duct. In 1953, the oral cholangiogram showed no visualization of the bile ducts.

CASE 29. G.W. was a female, aged 46 years, on whom in 1948, a cholecystectomy was performed for chronic cholecystitis and cholelithiasis. In 1950, a choledochoduodenostomy was done for recurrent colic, found to be due to obstruction of the common bile duct by an aberrant hepatic artery. In 1953, the oral cholangiogram showed no visualization of the bile ducts.

CASE 30. M.R., a female, aged 67 years, in 1938, had a cholecystectomy for cholelithiasis. Because of recurrent right upper quadrant pain a choledochoduodenostomy was performed in 1952. At this time a widely-dilated common duct was found, associated with a hypertrophic common duct sphincter. In 1953, the oral cholangiogram showed no visualization of the bile ducts.

CASE 31. J.J., a female, aged 58 years, had a cholecystostomy in 1915, with injury of the common bile duct. Because of recurrent jaundice, laparotomies had been done in 1915 and 1916, without relief of symptoms. In April, 1953, the patient came to the hospital because of recurrent jaundice, chills and fever. At that time a cholecystectomy was done for chronic cholecystitis and cholelithiasis. At the same time a choledochoduodenostomy was done for the relief of the biliary obstruction of traumatic origin, 38 years previously. Postoperatively the patient did well, with relief of the jaundice. In November the oral cholangiogram showed no visualization of the bile ducts.

Summary. The results of oral cholangiography in 31 post-cholecystectomy patients were:

Clinical Diagnosis	*No of Patients*	*Bile Ducts*		
		No Visual.	*Visual.*	*Dilated*
Dyskinesia	17	4	13	9
No symptoms	7	1	6	0
Choledochoduodenostomy	4	4	0	
Cystic duct remnant	3	0	3	1
Total	31	9	22	10

Conclusions. 1. Oral cholangiography is an easily-performed non-surgical procedure of practical diagnostic value.

2. Indications for its use are: (1) The post-cholecystectomy syndrome, and (2) non-visualization of the gallbladder.

3. The bile ducts have been visualized in approximately 85% of post-cholecystectomy patients studied to date, exclusive of those having a subsequent choledochoduodenostomy.

4. With biliary dyskinesia, about 70% of the bile ducts visualized were found dilated.

5. In post-cholecystectomy patients without symptoms, none of the bile ducts were significantly dilated.

6. Pathologic conditions such as cystic duct remnants can be detected by this method.

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ATTEMPTED SUICIDE WITH INSULIN

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Considering the many thousands of diabetics taking insulin, it is noteworthy that there have been only rare instances of suicide or attempted suicide with the drug. In a thorough search of the literature there were found just 6 papers describing a total of 8 cases of attempted suicide with insulin. Of these, 3 were fatalities and 5 recovered. All of them were insulin-treated diabetics who had had the disease for from 5 to 18 years. There were no nondiabetics noted.

I was called to see a nondiabetic physician who became unconscious without obvious cause, this later proving to be attempted suicide with insulin. It therefore seemed desirable to report his case both because of the rarity of attempted suicide by this means and also because the subject was a nondiabetic who took insulin with suicidal intent and complicated the picture by taking a large dose of morphine.

Previous Reports. Salient features of all reported cases are here reviewed. Massive doses of regular or protamine-zinc insulin were taken in all instances with one exception[8] in which only 20 units of insulin were taken with suicidal intent. The patient regretted his act, took sugar within 20 minutes and recovered promptly. Beardwood[1] reported the case of a 50-year-old diabetic woman who was found in pain and distress on the ground in a park. She hysterically told of taking 400 units of insulin with suicidal intent three-quarters of an hour previously. She was given dextrose and recovered. She normally took 52 units of insulin daily. Beardwood and Carmuth[2] later presented 2 other cases which illustrated the prolonged action and delayed effect of protamine-zinc insulin and also the importance of the administration of tremendous doses of glucose to counteract the hypoglycemic effect in dealing with severe reactions from protamine-zinc insulin. Their first case was a 27-year-old male diabetic who took 490 units of protamine-zinc insulin and became comatose 36 hours later. His usual daily dose of insulin was 50 units. On admission to the hospital his blood sugar was 33 mg. per 100 cc. It required 896 gm. carbohydrate to combat the insulin shock. It is significant that, despite repeated large injections of glucose solution, it was difficult to prevent a steady fall in the patient's blood sugar. Their second case was a 46-year-old female diabetic whose daily requirement was 7 units of regular insulin and 20 units of protamine insulin. She had threatened to commit suicide and her father found her at night on the floor, unconscious, cold and frothing at the mouth. An empty protamine-zinc insulin bottle, known to have been full that morning, was found beside the patient. On admission to the hospital, her blood sugar was 15 mg. per 100 cc. She was given intravenously 300 gm. of glucose as a 50% solution within 3 hours and the blood sugar rose to 32 mg. In the subsequent 12 hours she received an additional 500 gm. of glucose by vein, and more glucose was given in the next 24 hours before she finally recovered. Another interesting point in both cases is that, notwithstanding high blood sugar levels of about 300 mg. per 100 cc. after therapy, the patients remained uncon-

scious for some hours. However, they recovered without brain damage.

The largest known amount of insulin taken with suicidal intent was reported by Vogl and Youngwirth[9] who observed a 63-year-old male diabetic who had injected 2000 units of protamine-zinc insulin. His normal daily dose of protamine-zinc insulin was 40 units. The patient informed his wife at 5 p.m. that he had taken this enormous dose a short while previously. At this time, he had no unusual symptoms. A doctor, who was called at once, declared treatment was not necessary. Although not unconscious, he was taken to the hospital the following morning and was given glucose intravenously. The clinical course was characterized by great difficulty in attaining and maintaining a normal blood sugar level. This phenomenon persisted for 6 days in spite of almost continuous administration of glucose, 1425 gm. being given intravenously and 1400 gm. orally during this period. There was a tendency to hypoglycemia whenever therapeutic efforts were relaxed. For 6 days the patient had severe hypoglycemia, most marked on the third day, when the blood sugar was 10 mg. per 100 cc. and the patient lapsed into coma from which recovery was slow. It was 12 days before it became necessary to reinstitute insulin therapy.

Not all persons taking insulin with suicidal intentions recover. Joslin and associates[7] described 2 such cases. One was a 20-year-old female diabetic who took an unknown large quantity of insulin at home with suicidal intent. She was unconscious and remained so, dying 21½ hours after admission to the hospital, in spite of therapy. Postmortem examination showed cerebral edema. Their second case was a 29-year-old female diabetic who was found unconscious with 3 empty vials of U80 insulin and a syringe beside her bed. Her blood sugar was 27 mg. per 100 cc. Despite large doses of glucose, permanent cerebral damage developed with no return of higher cerebral function. She succumbed to pneumonia 4½ weeks later.

Gulzow[4], too, reported a case of a 39-year-old male diabetic who died after taking 400 units of regular insulin with suicidal intent. The onset of insulin shock appeared 4½ hours after taking the insulin, and one hour later therapy was instituted. He was given a total of 312 gm. of glucose intravenously and other supportive therapy, but he died 12½ hours after the administration of insulin. He normally had taken 54 units of regular insulin daily. Necropsy showed extensive intrameningeal hemorrhage with signs of increased intracranial pressure and edema of the brain which apparently caused the death. The liver showed cirrhosis with chronic hepatitis.

Case Report. The patient, a 46-year-old nondiabetic physician, had been relatively well physically. His past history was essentially negative. At 12:30 p.m. he told his nurse that he was not feeling well and that he was exhausted and drowsy. He lay down on his examining table and fell asleep. At 2:00 p.m. when I saw him, he was unconscious and could not be aroused. His nurse, who had been near him during the morning, could not explain this phenomenon.

Physical examination showed a well developed and nourished male who was in deep coma. The pulse was 78 and the blood pressure 160/86. Respirations were 16 per minute and normal in character. The skin was moist with much perspiration. There was some deviation of the eyes. The pupils were pin-point. The arms and legs were flaccid. The reflexes of arms and knee jerks could not be obtained. There was no Babinski. The heart, lungs and abdomen appeared normal.

In view of the pin-point pupils and coma, I felt that an overdose of sedative had been taken. On searching the office, an empty vial of Dilaudid and one of morphine were found in the wastebasket.

The patient was given 0.25 gm. of caffein sodium benzoate intramuscularly at 2:05 p.m.

and again at 2:20 p.m., but he still could not be aroused. Further search of his office was made and a 10-cc. vial of regular U80 insulin was seen on a table, not an unusual finding in a doctor's office. However, the nurse said he had brought it in that morning, but she knew of no patient who had needed it. I measured the amount of insulin in the bottle and found that 2.5 cc., or 200 units of insulin, were missing. On a long shot, his blood sugar was determined at 2:35 p.m. and found to be 42 mg. per 100 cc. I therefore felt that he had taken insulin. At 2:45 p.m. he was given 30 cc. of 50% glucose intravenously. When 15 cc. of the glucose had been injected, he moved around on the table, and when 30 cc. had been given, he could be aroused but was stuporous. He appeared astonished to be alive and wondered how I guessed what he had taken. He then admitted that he had taken 200 units of regular insulin, a vial of Dilaudid and one of morphine. While the preceding studies were made in the office, arrangements were made to send him to the hospital.

The patient was admitted to the New England Center Hospital at 3:45 p.m. At that time, he was semicomatose, but responded to painful stimuli. Blood pressure was 140/80, pulse 96, and respirations were 16 and normal in character. He was perspiring profusely. The pupils were still pin-point. The superficial and deep reflexes were present but weak, and there were no pathological reflexes. The cranial nerves appeared intact. The muscles were flaccid.

The blood sugar at 4:30 p.m. was 43 mg. per 100 cc. Other blood chemical findings at this time in terms of milliequivalents per liter were as follows: sodium, 148; potassium, 3.2; chloride, 100; and CO_2, 31.

Nalline (N-Allylnormorphine) has been used recently as an antagonist to morphine and Dilaudid poisoning[3,5]. To combat the narcotic poisoning in this case, 30 mg. of Nalline were injected intramuscularly at 4:45 p.m. Then 2000 cc. of 10% glucose in water solution were given as a continuous intravenous drip from 6 to 9:45 p.m. Shortly after glucose was started he became restless and could be aroused, and by 7:20 p.m. he recognized people. At 8:30 p.m. he vomited. From 9:45 to 11:45 p.m., 1000 cc. of 10% glucose in normal saline were adminstered intravenously. At 10:45 p.m. he was conscious and nauseated. The blood pressure was 140/80, pulse 76, and respiratory rate 16.

On the following day he vomited at 4 a.m. By 6 a.m. he was talkative and the blood pressure was 116/80. He took 300 cc. of orange juice at 10 a.m. At 1 p.m. he ate a good lunch and was in good spirits. From 3 to 11 p.m. he vomited much undigested food, but subsequently had no digestive disturbance. The blood pressure was approximately 116/80 during the next 2 days.

Laboratory data on the day after admission showed the following: Blood sugar 108 mg. per 100 cc., hemoglobin 98%, hematocrit 47% corpuscles, leukocytes, 12,700. The differential showed 70% neutrophils, 25% lymphocytes, 4% large mononuclears, 1% eosinophils. The urine was normal, although a specimen after the intravenous glucose contained some sugar. The sedimentation rate was normal. Hinton test was negative. Fishman test was negative. Stool was normal and there was no occult blood.

He was discharged in 2 days in good condition. It is interesting that in spite of the large doses of morphine (2¾ grains) and Dilaudid (9/20 grain) taken, the patient appeared not to be as ill as might be expected. This amount of narcotic usually causes a marked respiratory depression, yet this patient's respirations were normal. When asked why he took the morphine, he said that he wanted to mask the picture of insulin shock and prevent convulsions, thereby making it easier to die.

Comment. This case illustrates the importance of recognizing unconsciousness due to an overdosage of insulin so that treatment may be instituted promptly. Without early and sufficient therapy, insulin hypoglycemia may lead to irreversible tissue changes, particularly in the brain and heart, like those seen in anoxia. It is important to know the dose and type of insulin used, because the symptoms of insulin shock may appear within one or two hours after a large dose of regular insulin, in contrast to the much more prolonged period of 24 to 36 hours after the injection of a large dose of protamine-zinc insulin. It must be remembered, too, that the duration of the hypoglycemia varies with the size of the dose with the various types of insulin. Thus, the hypoglycemia is much more prolonged after protamine-zinc insulin than after regular insulin, since insulin is being liberated over a long period of time. Consequently, glucose therapy must be kept up for a much longer time

after protamine insulin shock than after regular insulin hypoglycemia.

It is difficult to predict the duration of the critical period and therefore the length of time during which vigorous therapy with glucose must be continued. For example, Vogl and Youngwirth's patient continued to have hypoglycemia up to the sixth day. Persons with hypoglycemic shock after regular insulin usually respond more readily and recover more rapidly than after protamine-zinc insulin. However, some may die.

It is noteworthy that in certain patients unconsciousness continues for some hours even with high blood sugar levels after glucose therapy, and some die because of the brain damage resulting from severe insulin shock. In non-fatal cases, the overdosage of insulin may result in permanent brain damage. The deleterious effect may continue after the blood sugar level has reached normal or above normal through intravenous glucose therapy. Tremendous doses of glucose may be required over a long period of time to combat such severe insulin reactions. This case, also illustrates the use and value of Nalline in the treatment of an excessive dose of narcotic. In view of the fact that this patient recovered from the narcotic poisoning so rapidly, the question might be raised as to whether insulin hypoglycemia modifies the effect of morphine. However, there is no recorded evidence of a possible antagonism between insulin and morphine or between insulin hypoglycemia and the metabolism of the drug, although insulin has been used in the treatment of narcotic addiction.

These facts may be of significance in this connection. According to Isbell[6], morphine depresses the output of 17-ketosteroids, and this depression is due, in part at least, to diminution in corticoid output by the adrenals. Whether this effect is directly on the adrenal gland and on the pituitary, or on the pituitary by some effect on the central nervous system, is unknown. On the other hand, very large doses of morphine have diphasic effects; first, depression and then stimulation of adrenal corticoid output. Cortisone and ACTH block some of the effects of morphine in rats. Insulin hypoglycemia causes stimulation of the pituitary adrenal axis and, in this way, might exert some antagonistic effect on morphine.

Summary. This paper presents a review of all the 8 recorded cases of attempted suicide with insulin (5 with recovery and 3 with fatal outcome), and reports the first case of a nondiabetic individual who so tried to commit suicide, using an injection of 200 units of regular insulin. The clinical picture was complicated by the large dose of morphine and Dilaudid which he took in order to disguise the symptoms of insulin shock and to prevent convulsions, so as to make it easier to die. The case illustrates the value of routine blood sugar estimation in the presence of coma. The treatment of self-induced insulin shock depends upon the type of insulin used as well as the dosage.

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SUCCESSFUL TREATMENT OF PNEUMOCOCCAL PNEUMONIA WITH COMBINATION OF CHLORAMPHENICOL AND PENICILLIN

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The theoretical as well as possible practical importance of antibiotic synergism and antagonism has aroused considerable interest. The original reports[3,4,7-13,18,19] were concerned with the effects of antibiotic combinations upon certain test organisms *in vitro* and their use in experimental infections in mice. In general these studies suggested that streptomycin frequently enhanced the bactericidal effect of penicillin. On the other hand, Aureomycin, chloramphenicol, and Terramycin appeared to diminish the useful effectiveness of penicillin alone. The successful use of combinations of penicillin and streptomycin in the treatment of subacute bacterial endocarditis[5,17] is an example of clinical results compatible with these observations. Recently Dowling[15] has reported that the use of a combination of Aureomycin and penicillin in a group of patients with pneumococcal meningitis was followed by a mortality rate distinctly higher than that seen in a comparable group of patients treated with penicillin alone. Further observations by Dowling *et al.*[6,16] in experimental pneumococcal infections in mice have shown apparent antibiotic antagonism under certain circumstances. However, Ahern and Kirby[1] were unable to demonstrate any interference of Aureomycin with the usual effectiveness of penicillin in patients with pneumococcal pneumonia. This report deals with the results observed in 50 patients with pneumococcal pneumonia treated with a combination of chloramphenicol and penicillin. The plan of treatment and dosage of antibiotics were specifically chosen to assess the possibility of antibiotic antagonism under practical clinical conditions.

Plan of Study. SELECTION OF CASES. The patients were unselected, consecutive admissions to the Third (New York University) Medical Division of Bellevue Hospital during the months from December, 1950, to June, 1951. Fifty patients in whom a definite clinical diagnosis of pneumococcal pneumonia could be established are the subjects of this report. In this group of 50 patients there occurred 52 episodes of pneumococcal pneumonia treated by a plan to be described. A small group of patients were excluded from the series because of therapy instituted prior to admission to the hospital. A further group of patients with acute bacterial pneumonia of other than pneumococcal etiology are not included in this report.

CRITERIA OF DIAGNOSIS. The diagnosis of pneumococcal pneumonia was made on the basis of the usual classical history of onset, characteristic physical signs, fever, leukocytosis, sputum smear, sputum culture, blood culture and Roentgen-ray findings of consolidation. In Table 1 are given the important, clinical, bacteriological, and therapeutic data on these patients.

AGE OF PATIENTS. The ages of the patients varied between 16 and 79 years, with over one-half of the patients in the fourth and fifth decades.

DATE OF ONSET OF INFECTION. In 35 instances the patients were admitted within 3 days of onset of the illness, as estimated from historical data. The remaining 15 patients were admitted within from 4 to 7 days of onset. In two the time of onset could not be established.

TYPES OF PNEUMOCOCCI. There were 37 patients from whom type-specific pneumococci were recovered. Pneumococci cultured from an additional 13 patients were not classified by typing.

TABLE 1.—CLINICAL DATA IN 50 PATIENTS TREATED IN 52 ATTACKS OF PNEUMOCOCCAL PNEUMONIA WITH CHLORAMPHENICOL AND PENICILLIN

GROUP I.: Chloramphenicol 1.0 gm. orally initially; Chloramphenicol 0.5 gm. orally and Penicillin 20,000 units intramuscularly every 6 hours thereafter.

									Bacteriology			Response			
Case	*Age*	*Sex*	*Days After Onset*	*Class. History* *	*Pulm. Consol.* **	*Lobes Involved*	*Adm. Temp. ° F.*	*W.B.C. ÷1000*	*Smear*	*Sputum*	*Blood*	*Immed. Hrs.*	*Time to Normal T.*	*Days of R*	*Complications*
1	28	F	1	Yes	Yes	RUL	102.4	25.0	Pos.	Pn. IV	Neg.	12	6 d	8 d	Syphilis, Anemia, Alcoholism
2	63	M	—	—	Yes	RLL	102	16.8	Pos.	Pos.	Neg	0	9 d	9 d	Icterus
3	42	F	2	Yes	Yes	RLL	102.4	16.5	Pos.	Pos.	Neg.	24	36 h	6 d	Pregnancy
4	48	M	2	Yes	Yes	RML RLL	102	15.0	Pos.	Pn. V	—	48	6 d	5 d	
5	52	M	4	Yes	Yes	RLL	101.2	14.0	—	Pn. III	Neg.	0	5 d	7 d	Cirrhosis, Alcoholism
6	61	M	2	Yes	Yes	RML	101.4	15.4	Pos.	Pos.	Neg.	48	48 h	8 d	
7	17	F	2	Yes	Yes	LLL	101	19.4	Pos.	Pn. II	—	24	24 h	4 d	
8	55	F	3	Yes	Yes	LLL RLL	103.8	14.1	Pos.	Pos.	Neg.	12	36 h	5 d	
9	62	F	3	Yes	Yes	LLL	104.2	8.8	Pos.	Pos.	Neg.	12	5 d	7 d	
10	47	F	6	Yes	Yes	RUL	105	28.5	Pos.	Pn. XXV	—	12	4 d	7 d	Diabetes Mellitus
11	74	M	3	Yes	Yes	LLL	103	10.0	Pos.	Pn. XVIII	Pn. XVIII	24	48 h	7 d	Anemia
12	24	F	1	Yes	Yes	RLL	103	17.5	Pos.	Pn. IV	Neg.	24	48 h	6 d	Alcoholism
13	40	M	1	Yes	Yes	RUL	104.4	30.0	Pos.	Pn. IV	—	12	24 h	6 d	Alcoholism
14	31	F	—	—	Yes	RUL	102	29.5	Pos.	Pos.	Neg.	12	24 h	5 d	Anemia, Pregnancy
15	48	F	5	Yes	Yes	LLL	102.6	14.4	—	Pos.	Neg.	12	4 d	4 d	Hepatomegaly
16	38	F	3	Yes	Yes	LLL	101	8.9	—	Pn. XIV	Neg.	0	4 d	4 d	
17	47	M	2	Yes	Yes	RLL	104	20.6	Pos.	Pn. XX	Neg.	12	48 h	7 d	
18	23	F	2	Yes	Yes	RML RLL	105	17.4	Pos.	Pn. IV	Neg.	12	24 h	6 d	
19	39	M	3	Yes	Yes	RUL	102.8	21.2	Pos.	Pos.	Neg.	12	6 d	4 d	
20	42	M	3	Yes	Yes	LLL	104.2	11.0	—	Pn. II	Pn. II	24	48 h	5 d	Alcoholism
21	45	F	1	Yes	Yes	RLL	104	42.6	Pos.	Pos.	Pn. XX	12	24 h	4 d	
22	58	M	4	Yes	Yes	RUL	103.6	29.0	Pos.	Pos.	Neg.	12	48 h	3 d	
23	53	M	3	Yes	Yes	RLL	103	18.5	Pos.	Pos.	Neg.	24	48 h	7 d	
24	41	M	2	Yes	Yes	LLL	105.4	44.2	Pos.	Neg.	Neg.	12	3 d	6 d	
25	47	M	3	Yes	Yes	RML	102	19.4	Pos.	Neg.	Pn. VII	12	48 h	7 d	
26	28	M	3	Yes	Yes	LLL	103.6	19.5	Pos.	Pn. VIII	Pn. VIII	12	36 h	6 d	
27	42	F	5	Yes	Yes	RML	104.2	16.5	Pos.	Neg.	Pn. I	0	12 d	12 d	Sterile Empyema
28	49	M	1	Yes	Yes	LLL RML	102.4	27.5	Pos.	Pn. VIII	Neg.	12	5 d	7 d	
29	16	F	6	Yes	Yes	LLL	102.4	19.2	Pos.	Pn. V	—	24	4 d	7 d	
30	59	M	2	Yes	Yes	RLL	101	17.0	—	Pn. II	—	0	3 d	2 d	
31	46	M	7	Yes	Yes	RLL LLL	100.2	10.2	—	Pn. XXIV	Neg.	0	6 d	6 d	Alcoholism

TABLE 1.—*Continued*

Case	Age	Sex	Days After Onset	Class. History *	Pulm. Consol. **	Lobes Involved	Adm. Temp. ° F.	W.B.C. ÷1000	Bacteriology			Response			Complications
									Smear	Sputum	Blood	Immed. Hrs.	Time to Normal T.	Days of R	
32	54	M	1	Yes	Yes	RLL	101	13.5	Pos.	Pn. VIII	Pn. VIII	0	7 d	8 d	
33	54	M	1	Yes	Yes	RLL	105	34.2	Pos.	Pn. XII	Pn. XII	24	6 d	6 d	Cardiac: ASHD
34	48	M	4	Yes	Yes	LLL	103.8	9.9	Pos.	Pn. VI	Neg	24	6 d	7 d	
35	52	M	2	Yes	Yes	RML	101	14.5	Pos.	Pn. VIII	Neg.	24	24 h	10 d	
36	48	F	4	Yes	Yes	RUL,RML RLL	102	47.5	Pos.	Pos.	Neg.	0	48 h	7 d	Alcoholism
37	53	M	2	Yes	Yes	LLL	103	9.7	Pos.	Pn. V	Neg.	0	7 d	6 d	
38	33	F	2	Yes	Yes	LLL	105	9.3	Pos.	Pn. XIX	Neg.	24	3 d	8 d	
39	46	F	1	Yes	Yes	RLL	102	16.0	Pos.	Pn. III	Neg.	12	24 h	2 d	
40	42	M	1	Yes	Yes	RUL	—	21.5	Pos.	Pn. XXIV	Neg.	24	7 d	7 d	
41	25	F	1	Yes	Yes	RLL	102	14.0	Pos.	—	Neg.	12	12 h	4 d	AOR—4th day
			2	Yes	Yes	RML RLL	104.4	26.0	Pos.	Pn. IV	Pn. IV	24	24 h	7 d	Readmitted 5 days later; Acute Glomerular Nephritis
42	35	M	6	Yes	Yes	RML RUL	103.4	22.5	Pos.	Pn. VII	Pn. VII	24	6 d	6 d	
43	20	F	7	Yes	Yes	RLL	104.4	25.6	Pos.	Pos.	Neg.	24	48 h	4 d	Pregnancy
44	42	M	5	Yes	Yes	LLL	103.8	13.1	Pos.	Pn. VI	Neg.	48	72 h	5 d	Diabetes Mellitus Discharged 7th day
			6	Yes	Yes	LLL	104	13.5	Pos.	Pos.	Neg.	48	5 d	6 d	Discharged 7th day
			1	No	Yes	RLL LLL	103	16.6	Pos.	Pos.	Neg.	0	—	6 hr.	Readmitted 1 day later. Purulent meningitis; Intensive antibiotic R, apparent recovery. Died 4 months later
			Group II.: Chloramphenicol 1.0 gm. orally initially; Chloramphenicol 0.5 gm. orally and Penicillin 100,000 units intramuscularly every 6 hours thereafter.												
45	42	M	4	Yes	Yes	RUL RML	103.2	21.4	Pos.	Pn. VII	Neg.	12	4 d	7 d	
46	56	M	1	Yes	Yes	RML RLL	103	25.0	Pos.	Pn. III	Neg.	24	4 d	9 d	Alcoholism
47	28	F	3	Yes	Yes	LLL	104.8	4.5	Pos.	Pn. XVIII	Neg.	0	4 d	8 d	Alcoholism, Anemia, Syphilis
48	57	F	1	Yes	Yes	LLL	101.6	16.5	Pos.	Pn. XIX	Neg.	12	6 d	7 d	Cardiac: RHD
49	50	M	1	Yes	Yes	RLL	103.4	15.2	Pos.	Pn. VII	Pn. VII	24	48 h	6 d	Alcoholism
			Group III.: Chloramphenicol 1.0 gm. orally initially; Chloramphenicol 0.5 gm. orally and Penicillin 300,000 units intramuscularly every 6 hours thereafter.												
50	18	M	5	Yes	Yes	RLL	103	24.5	—	Pn. XXIV	Neg.	12	12 h	8 d	Chronic Glomerular Nephritis

Key: * Classical History refers to the presence of at least 2 of the 3 following characteristic symptoms: abrupt onset, shaking chills, and rusty sputum.
** Pulmonary Consolidation refers to frank consoldiation as demonstrated by either or both physical examination and Roentgen-ray.

The types of pneumococci isolated are shown in the following table (Table 2):

TABLE 2.—TYPES OF PNEUMOCOCCI ISOLATED FROM 50 PATIENTS IN 52 ATTACKS OF PNEUMONIA

Type	*No. of Patients*	
I	1	
II	3	
III	4	25 cases
IV	4	
V	3	
VI	2	
VII	4	
VIII	4	
IX through XIX	5	
XX through XXIX	7	
Not Classified	13	
Total	50	
Negative cultures	2	

It can be seen that in 25 cases the pneumococci were Types I to VIII, which most frequently give rise to severe pneumonia.

BACTEREMIA. The initial blood culture was positive in 11 (22%) instances. This incidence would appear to be comparable to previously reported series of cases studied here[21] and at other institutions[1].

METHOD OF TREATMENT. Each patient received an initial oral 1.0 gm. priming dose of chloramphenicol. No penicillin was administered with this dose. After 6 hours, each patient was given concomitant doses of chloramphenicol and penicillin. The subsequent doses of chloramphenicol were 0.5 gm. at 6-hour intervals. In 46 instances, penicillin was given in a dosage of 20,000 units intramuscularly every 6 hours. This level was selected to supply a minimal but effective dose of penicillin. However, in 5 patients the penicillin dosage was 100,000 units every 6 hours; in one case, the dosage was 300,000 units every 6 hours.

Results of Treatment. RESPONSE TO TREATMENT. The patients were examined daily. The physical findings, Roentgen-ray findings, and temperature were used to evaluate the therapeutic response.

An immediate response to treatment is considered to be a sustained drop of temperature of 2 degrees below the admission temperature, occurring within the first 48 hours. Forty-two (80.7%) patients showed a good initial response. Twenty-one responded within 12 hours of admission; another 17 responded within 24 hours and 4 within 48 hours.

The number of days required for each patient to react and sustain a normal temperature are recorded. In 24 (46%) patients, this occurred within 48 hours. In the remaining 28 instances, normal temperature was reached within 3 to 12 days.

COMPLICATIONS. The following specific complications occurred. One patient developed a sterile empyema which responded promptly to the intrapleural use of streptokinase-streptodornase. An additional patient showed a sterile pleural effusion.

One patient had a recurrence of pneumonia 5 days after leaving the hospital against advice on the fourth day of hospitalization, after only 4 days of treatment from the onset of the illness. On readmission there was a prompt and sustained response within 24 hours following treatment with the same combination of antibiotics.

Slow resolution as demonstrated by physical examination and Roentgen-ray occurred in 5 patients (9.6%).

DEATHS. There was only one death in the series. This patient had recurrent episodes of lobar pneumonia due to pneumococcus. These separate episodes seemed to respond to a combination of chloramphenicol and penicillin on two occasions. The patient returned 24 hours after this second episode with frank meningitis and pneumonia which responded slowly to large doses of penicillin, sulfadiazine, streptomycin, and Aureomycin. After 3 months of apparent good health this patient was readmitted and died 3 days later. The exact cause of death was obscure, but the clinical diagnosis was brain abscess or recurrence of pneumo-

coccal meningitis. This patient must be considered a possible treatment failure.

NONSPECIFIC COMPLICATIONS. Since these were unselected patients of varying ages from a group treated in a large municipal hospital, it is not surprising that there were a variety of complicating pre-existing disease states.

Twenty-two patients showed one or more of the following conditions: alcoholism, 10; anemia, 4; icterus, 1; cirrhosis, 2; renal disease, 3; syphilis, 2; pregnancy, 3; cardiac disease, 2; and diabetes mellitus, 2.

In several of the patients who showed slow resolution of the pneumonic process and also in others an underlying bronchiectasis was suspected. Since no special studies were undertaken to establish this diagnosis no attempt has been made to assign a role to underlying bronchiectasis or other chronic pulmonary disease in the responses observed.

Discussion. The successful and satisfactory treatment of pneumococcal pneumonia with a combination of chloramphenicol and penicillin is reported. Forty-two patients (80.7%) showed a good immediate response and 24 (46%) showed a sustained normal temperature after 48 hours. The incidence of specific complications was low. There were 5 cases (9.6%) of slow resolution with eventual clearing. There were two instances of recurrence of pneumonia. One case was inadequately treated and had left the hospital against advice. The second recurrence developed 24 hours following discharge and was accompanied by purulent meningitis. This patient's subsequent death 3 months later must be considered a possible treatment failure.

An evaluation of the effectiveness of this combination of agents can be made by comparison with a similar series of patients treated with comparable doses of chloramphenicol or penicillin alone. There are relatively few reports in the literature of the response of pneumococcal pneumonia to chloramphenicol alone, but in two series[2,14] the results have been good. It is necessary to compare our results with a much earlier series of patients treated with comparable doses of penicillin alone. In a similar series[21] of patients at Bellevue Hospital, a favorable and definite response was observed in 84.6%, while an equivocal response occurred in 9.1%. The total mortality was 6.3%. It is apparent that the type of response, incidence of complications and the mortality are alike. Furthermore, our series is entirely comparable to that of Ahern and Kirby[1] who reported the successful treatment of pneumococcal pneumonia with a combination of Aureomycin and penicillin.

In reviewing the numerous experimental studies of the last few years in an effort to relate these observations to practical clinical situations, a number of factors immediately warrant consideration and discussion. In many of the original experiments only single, rather than multiple, doses of antibiotics were used. This has not been true of all, particularly the more recent, experimental work reported. It is apparent that there is a relatively sharply restricted range of dosage in which interference occurred. This antagonistic effect was conditioned both by the actual amounts of antibiotics used, but also by the ratio of one to the other. These quantitative factors differed considerably in *in vitro* as compared to *in vivo* experiments. Furthermore, the results observed were contingent upon the species of bacterium used as the test organism, and in some cases there were even individual strain differences. In the situations where antagonism has been demon-

strated, one agent has appeared to act unfavorably upon the other, but the second agent has not appeared to affect the first. For example, where chloramphenicol has interferred with the action of penicillin, the penicillin has not appeared to interfere with the action of chloramphenicol. It is believed that this has resulted from the bacteriostatic effect of one drug which interferes with bacterial multiplication and thus nullifies the effect of the second drug. A similar but different set of conditions appears to exist in the demonstration of synergistic effects.

In the light of the relatively restricting and detailed conditions required for the *in vitro* or *in vivo* demonstration of antagonism or synergism, the treatment of a patient with a particular bacterial infection by a combination of two antibiotics becomes quite complicated. The size of the individual doses, the route of administration, their timing in relation to each other, the relative rates of absorption of each antibiotic and their distribution in the tissues, and the constantly shifting relationship of these concentrations in the tissues all assume importance. This point has been thoroughly discussed by Tillett[20] and he concludes that in order for the exacting experimental conditions of antagonism of two antibiotics to be fulfilled in the patient, a high degree of improbability exists. He states that it is only in certain localized types of infections with the local use of exact antibiotic concentrations where the conditions can be more closely approximated. Furthermore, factors of host resistance, both cellular and immunological, play a significant role in almost all infections and since their role is often difficult to measure, the possibility of antibiotic antagonism or synergism is rendered even more difficult of evaluation.

In the plan of therapy used, it was our aim to obtain an initial effect of chloramphenicol by the use of an adequate oral dose and to continue with simultaneous adequate oral doses of chloramphenicol and adequate but minimal intramuscular doses of penicillin.

It is patently impossible to attempt to estimate the concentrations of each antibiotic on the described dosage schedule, or to estimate the ratio of the concentration of one agent to the other. Therefore, it is futile to speculate as to the possibility that in a hypothetical case of pneumonia, comparable to the actual cases of this series, there exist the exacting conditions resulting in antibiotic antagonism. However, as pointed out by Tillett[20], it probably is highly unlikely.

The use of a combination of chloramphenicol and penicillin by the method and dosage described demonstrated neither a lack of response in less than the expected number nor any marked delay in response. The study reported was undertaken solely for the purpose of evaluating the possible appearance of antibiotic antagonism by the use of a combination of chloramphenicol and penicillin. It is emphasized that the use of such a combination is not regularly necessary and is not recommended as a routine form of treatment.

Summary. This report summarizes the results observed in the treatment of 52 episodes of pneumococcal pneumonia in 50 patients treated with a combination of chloramphenicol and penicillin.

A definite, immediate response occurred in 42 (80.7%) patients and a slower response occurred in the remainder. The incidence of specific complications was low; there was one delayed death (3 months later from

brain abscess or meningitis) which must be attributed to treatment failure.

In view of the adequate response observed, no antagonism from the use of a combination of the two antibiotics was apparent.

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NEO-PENIL: A COMPARATIVE STUDY OF BLOOD, URINE AND LUNG LEVELS

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Considerable attention has been focused recently upon the ability of Neo-Penil, the diethylaminoethyl ester hydriodide of penicillin G, to concentrate in certain tissues of the body. One of the original observations made by Jensen and his associates[3] was that this ester diffuses readily into lungs and concentrates at levels significantly higher than in the serum. This unique property has likewise been demonstrated in man[2,4]. The potential value of such an agent in the therapy of pulmonary infection is obvious. It was therefore decided to study further the ability of this agent to concentrate in the lungs of man. Since the concentration of penicillin in a given tissue is related to its concentration in the blood stream, it appeared worthwhile to run a preliminary study on blood level concentrations and renal excretion rates in patients receiving various doses of Neo-Penil and procaine penicillin. Procaine penicillin was compared with Neo-Penil because of its similar depot effect[1,3,4]. In the plasma and lung level study, aqueous penicillin G was likewise included for comparison.

Material and Methods. BLOOD LEVEL STUDIES. In the preliminary blood level studies, 3 groups of 6 patients on the medical ward were selected for each of the 3 doses studied; namely, 300,000, 500,000, and 1,000,000 units given as single intramuscular injections. No patients were chosen who showed clinical evidence of heart failure, renal failure, liver failure, acute disease of liver, or edema due to other causes. In the main, they led bed-chair existences during the study. Each patient served as his own control in that each received Neo-Penil* and procaine penicillin alternately at intervals of at least 48 hours between each preparation. Blood specimens were drawn at one, 2, 4, 8, 12, 16, and 24 hours after injection of the drug. Fractional urine collections were made at 4-hour intervals throughout the 24-hour period. Plasma (removed from the heparinized blood) and urine specimens were refrigerated until assay on the following day. *Sarcina lutea* was used as the test organism in assaying plasma and *B. subtilis* in assaying urine.

TISSUE LEVEL STUDIES. Following this first study, determinations of normal lung tissue levels were made on patients who were being operated on for cardiac or pulmonary disease. One group of these patients received 600,000 units of either Neo-Penil, procaine penicillin or aqueous penicillin G approximately one hour before surgery. The second group likewise received 600,000 units of one of the 3 penicillin preparations approximately 12 hours before surgery. At the time of surgery, a 5 gm. biopsy specimen of the periphery of an upper lobe was excised following the definitive operative procedure. At the same time a specimen of blood was with-

*The Neo-Penil used in this study was generously supplied by Smith, Kline & French Laboratories.

drawn for assay. Each lung specimen was examined grossly by one of us, before it was accepted as normal. Each tissue was weighed and macerated in a Waring blendor with 4 parts of phosphate buffer (pH 6.0) and assayed. All penicillin assays were carried out by the cup-plate method[5] with the substitution of paper disks for cylinders.

Results. BLOOD LEVEL STUDIES. The average plasma penicillin levels on the 3 groups of individuals, alternately receiving the varying doses of Neo-Penil and procaine penicillin, are shown in Table 1. It is apparent that Neo-Penil, like procaine penicillin, has a definite depot effect. The average plasma levels at any given time, however, are higher with procaine penicillin. The lower plasma levels obtained with Neo-Penil correlate with a decreased excretion of penicillin in the urine. Regardless of the dose administered, the penicillin recoverable in urine following administration of procaine penicillin is about double that following the administration of Neo-Penil. The percentage recoveries of the total administered dose for the former varied from 44 to 51%, and for Neo-Penil from 21 to 29%.

TABLE 1. COMPARATIVE PLASMA LEVELS IN PATIENTS RECEIVING NEO-PENIL AND PROCAINE PENICILLIN

		*Average Plasma Levels, units/cc.**						
Dosage	*Penicillin*	*1 hr.*	*2 hrs.*	*4 hrs.*	*8 hrs.*	*12 hrs.*	*16 hrs.*	*24 hrs.*
300,000	Neo-Penil	.46	.49	.33	.23	.11	.07	.012
	Procaine	.93	1.24	1.06	.61	.38	.20	.033
500,000	Neo-Penil	.93	1.21	1.14	.61	.23	.05	.0
	Procaine	1.33	1.74	1.36	.65	.42	.32	.12
1,000,000	Neo-Penil	.73	1.32	1.05	.62	.48	.26	.15
	Procaine	.95	2.00	1.26	.82	.67	.52	.42

* Average of 6 patients

TISSUE LEVEL STUDIES. The blood and lung levels of patients receiving either Neo-Penil, procaine penicillin, or aqueous penicillin G one hour or 12 hours before surgery are shown in Tables 2 and 3. For obvious reasons, it was not always possible to obtain specimens exactly one hour or 12 hours after the administration of the appropriate penicillin. The variation was not more than 30 minutes in the one-hour cases and 90 minutes in the 12-hour cases. The plasma levels following administration of each of the 3 different preparations are essentially the levels one would anticipate. However, one hour after injection, in spite of the lower plasma levels, Neo-Penil achieved higher lung levels than did aqueous or procaine penicillin. The Neo-Penil lung levels are approximately twice as high as its plasma levels. Conversely, the procaine and aqueous penicillin lung levels are about one-half as high as their plasma levels.

In the group of patients receiving the different preparations of penicillin 12 hours before surgery, the lung levels following Neo-Penil continue to show a higher concentration than after procaine or aqueous penicillin. One may observe, also, that whereas the plasma levels after Neo-Penil and procaine penicillin are approximately the same, the lung levels after Neo-Penil are considerably higher. Of particular interest in this respect, as shown in Table 4, is the greater number of lung specimens showing detectable levels, at this

TABLE 2.—COMPARATIVE PLASMA AND LUNG LEVELS (UNITS/GM.) ONE HOUR AFTER ADMINISTRATION OF 600,000 UNITS OF THREE PENICILLIN PREPARATIONS

Neo-Penil			*Procaine Penicillin*			*Aqueous Penicillin*		
No.	*Plasma*	*Lung*	*No.*	*Plasma*	*Lung*	*No.*	*Plasma*	*Lung*
9	1.80	1.23	3	2.45	.53	4	1.30	.50
11	.59	1.20	33	2.90	.48	7	2.18	.72
16	1.45	3.15	34	.48	.39	12	4.70	2.57
19	1.05	4.00	35	2.48	.74	13	5.20	2.63
21	.94	<.35	36	1.19	2.05	14	4.20	1.85
22	1.23	5.00	39	1.15	.46	15	2.90	1.49
23	.94	<.35	41	.68	.30	17	1.55	1.25
24	1.60	4.30	42	.85	.34	18	1.53	1.24
25	.25	4.90	43	.53	1.29	26	2.00	1.40
27	1.20	1.40	47	1.06	.60	28	1.63	1.50
29	1.55	6.75				30	3.20	1.60
31	.17	1.60						
32	1.50	5.15						
37	.94	1.20						
40	1.03	2.10						
48	.73	.85						
51	.65	1.10						
87	.35	2.90						
88	1.40	.53						
89	1.15	1.20						
91	1.07	2.15						
Av.	1.07	2.41	Av.	1.38	.72	Av.	2.76	1.52

TABLE 3.—COMPARATIVE PLASMA AND LUNG LEVELS (UNITS/GM.) TWELVE HOURS AFTER ADMINISTRATION OF 600,000 UNITS OF THREE PENICILLIN PREPARATIONS

Neo-Penil			*Procaine Penicillin*			*Aqueous Penicillin*		
No.	*Plasma*	*Lung*	*No.*	*Plasma*	*Lung*	*No.*	*Plasma*	*Lung*
54	.76	2.05	67	.86	<.30	95	.36	<.15
56	.06	.25	79	.81	<.30	111	.04	<.15
57	1.02	.89	80	.70	.50	112	.03	<.15
64	.62	.44	82	.75	<.30	123	.25	<.15
65	.60	.30	84	.32	<.30	124	.21	.73
66	.92	.60	85	.48	<.30	125	.04	.35
70	1.33	<.30	100	.89	.25	126	.08	<.15
71	.44	.41	101	1.93	.34	128	.10	.17
73	.80	.41	102	.23	<.15	129	.05	.58
75	.80	.38	104	.22	<.15	130	.18	.26
77	.71	.38	106	.19	<.15	131	.38	<.15
81	.48	.40	110	.69	.17	132	.26	.34
68	.73	.44	113	.75	.38	134	.05	<.15
69	.43	<.30				135	.30	<.15
						136	.41	<.15
						137	.15	<.15
						138	.24	<.15
						139	.08	<.15
						140	.03	<.15
						144	.73	.37
						145	.26	<.15
						146	.19	<.15
						147	.13	.58
						148	.12	.42
						150	.10	.17
Av.	.70	.49	Av.	.68	.13	Av.	.19	.16

time, with Neo-Penil than with the other two preparations.

During the course of this study, 681 injections of Neo-Penil were administered to 396 patients. There were no significant immediate or delayed (24 hours), local or systemic reactions noted.

Discussion. In general, the data obtained in these studies confirm the reports of Jensen and others. Although the plasma levels obtained in patients receiving Neo-Penil are not as high as the levels obtained with procaine penicillin, Neo-Penil has a definite repository effect. The lower plasma levels correlate with decreased urinary recovery. This fact is probably related to the preferential localization of this agent in various tissues of the body. Flippin *et al.*[1] have recently reported increased spinal fluid levels in patients receiving Neo-Penil. Rhodes *et al.*[6] have likewise shown that the ester concentrates in the lymphatic tissues of animals. The evidence presented in this paper indicates the greater ability of Neo-Penil to concentrate in the lungs of man.

In view of the increased levels in lung tissue, one is probably justified in assuming increased clinical effectiveness of this agent in therapy of some pulmonary infections. This would be particularly true of infections due to organisms commonly considered to be relatively resistant to penicillin. The increased levels might be sufficient to eradicate an infection due to a penicillin resistant staphylococcus, enterococcus, or possibly a Gram-negative bacillus. Further clinical trials are certainly indicated. Because of its prolonged localization in the lungs, Neo-Penil should prove of considerable value in thoracic surgery, in the prevention of post-surgical infection.

It was not the intent of the authors, at this time, to study the mechanism of action of this agent. It is apparent that further studies are needed before one may elucidate the factors surrounding its specific tissue localization. Our series of cases includes only normal lung specimens. Ungar and Muggleton[7] have recently reported that, in animals the levels with the ester are higher in inflamed lung tissue than in normal lung tissue. This observation could account for the higher lung levels reported by Jensen and associates[3,4] who studied only abnormal lung tissues.

TABLE 4.—INCIDENCE OF LUNG TISSUES HAVING DETECTABLE LEVELS, 12 HOURS AFTER ADMINISTRATION

Preparation	*No. of Cases*	*Detectable Levels**	
		No.	*%*
Neo-Penil	14	12	86
Procaine	13	5	38
Aqueous	25	10	40

* Minimum detectable concentration — .15 to .35 units/gm.

Summary. Neo-Penil, the diethylaminoethyl ester hydriodide of penicillin G, has a repository action similar to that of procaine penicillin, although its plasma levels are somewhat lower. The urinary recovery rates of the ester are about one half those of the latter penicillin. Concentration of penicillin in the lung tissue of patients injected with Neo-Penil greatly exceeds that of similar patients receiving procaine or aqueous penicillin G. The potential value of this agent in the therapy of lung infections is discussed.

ACKNOWLEDGMENTS. The authors wish to express their deepest apprection to their colleagues, Dr. Charles P. Bailey, Dr. J. Antrim Crellin, Dr. Robert P. Glover, and Dr. Thomas J. O'Neill, without whose assistance and cooperation this study would not have been possible. We are also indebted to the tireless and efficient efforts of our technical associates, Miss Florence Paff, Morton Fuchs, M.D., and Morton Mallin.

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EXPERIENCE WITH THE RADIOIODINE TRACER TEST IN RADIOIODINE-TREATED THYROTOXIC PATIENTS

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Two important problems in treating thyrotoxicosis are related, on the one hand, to the determination of the types of thyrotoxicosis which will respond best to a given form of therapy and, on the other to the decision following therapy that the disease in a given patient is under adequate control. In regard to the second problem, one might infer from the literature that the radioiodine tracer study is not only a valid diagnostic tool in thyroid problems but may be an equally useful test for following the course of a patient treated with radiation for thyrotoxicosis. Colby and Williams[2] found that external irradiation of the thyroid in euthyroid subjects decreased the iodide-accumulating capacity of such thyroids. Freedberg and associates[3] noted the expected tracer study values in myxedematous and euthyroid cardiac patients who had received radioiodine therapy for angina pectoris. They suggested, in another study, that radioiodine-treated thyrotoxic individuals may continue in the thyrotoxic state but nonetheless exhibit a high normal uptake[4]. Presumably these patients originally had uptake values in the usual thyrotoxic range. Soley and associates[8], however, noted an occasional elevated radioiodine uptake in subjects who were euthyroid after radioiodine therapy. And the reports of Werner *et al.*[9,10] state that the same range of normality holds for the tracer test before and after radioiodine therapy. In regard to the first problem noted above, there are conflicting reports in the literature concerning the advisability of using radioiodine in treating patients with multinodular goiter and associated thyrotoxicosis[5,7]. The inadvisability of such treatment is predicated, in part, on the idea that excessive amounts of radioiodine are needed in such patients.

The following study was planned as an attempt to clarify the interpretation of the tracer study after radioiodine treatment. We also thought that it might help to explain the discrepancies in the literature regarding the choice of patients best suited for radioiodine therapy.

Method. Tracer studies utilizing radioiodine were carried out on 45 unselected thyrotoxic patients treated with radioiodine in the Radioisotope Clinic at the Cincinnati General Hospital. These studies were performed as soon after such treatment as was technically possible.

In this laboratory euthyroid patients are found to have a 24-hour uptake range of 19 to 77%, with only an occasional result outside of the range of 20 to 60%. This latter range also contains about 10% of the thyrotoxic subjects studied. Thyrotoxic patients studied in this laboratory show a 24-hour uptake range of 54% to more than 100%, with about 10% of the results below 61%; practically all values are in excess of 50%.

The ranges we accept therefore are: (1) thyrotoxic, anything above 60% uptake; (2) borderline, from 50 to 60% uptake; and (3) euthyroid, 20 to 50% uptake. Patients with myxedema have had uptake values ranging from 0 to 38%. However, no euthyroid pa-

tient has demonstrated an uptake value of less than 19% except in those instances where a history of recent ingestion of iodine in some form was obtained. The myxedema range is therefore considered any uptake less than 19%, knowing that a number of myxedematous patients will not test within this range.

It should be mentioned that our "*in vivo*" counting method has a back-scatter error of approximately 20%, so that high uptake values have an appreciable associated numerical error; occasionally we will record an uptake of approximately 115%. All of the values herein reported are uncorrected. This error is not present in our urine-counting method, and experience in this laboratory has shown that the 48-hour urine value ranges are: (1) thyrotoxic, 0 to 40%; (2) borderline, 40 to 50%; (3) euthyroid, 50 to 70%; and (4) myxedema, over 70%. It is rare to find a euthyroid patient who has not recently received iodine and who excretes more than 70% of a tracer dose within 48 hours.

Results. The results of this study are listed in Table 1. Group A consists of patients who, after treatment with radioiodine for thyrotoxicosis, were still clinically thyrotoxic. Group B consists of similar patients who clinically were euthyroid. Group C consists of like subjects who were considered myxedematous. The clinical evaluation of these patients was derived from a combination of careful repeated examinations by the author and of frequent determinations of the basal metabolic rate.

In Group A, 19 tracer studies were performed on 12 patients. The 24-hour uptake determinations in 12 of the studies fell within the usual thyrotoxic range: five of the 12 values were significantly lower than pretreatment values in the same patients. Uptake determinations in 3 others of the 19 studies were in the borderline range. In 3 other tracers uptake values were normal; while in one the value was close to zero. Forty-eight hour excretion determinations in 7 of 18 studies were in the usual thyrotoxic range and no value was significantly lower than

TABLE 1.—RESULTS WITH RADIOIODINE TRACER TEST IN 45 THYROTOXIC PATIENTS BEFORE AND AFTER RADIOIODINE THERAPY

	Post-Therapy Tracer			*Pre-Therapy Tracer*	
Patient	*24-hr. Uptake (%)*	*48-hr. Urinary Excretion Days, 1; 2 (%)*	*Interval Between Therapy & Tracer (months)*	*24-hr. Uptake (%)*	*48-hr. Urinary Excretion Days, 1; 2 (%)*
			A. Still Toxic Clinically		
1. I. H.	76	41;6	3	93	23;8
	68	30;3	13		
2. L. A.	57	—;—	13	—	9.5;4
	57	52;0	19		
3. J. Y.	54	30;2	6	68.5	41;3
4. M. B.	78	18;—	5	101	14;0
5. F. B.	106	3;2	3	97	19;0
	65	38;10	8 (after 2nd therapy)	106	3;2
6. M. D.	8	62;8	3	114	2;2.5
7. A. P.	34	44;12	3	70	30;3
8. D. K.	63	51;7.5	3	69	30;1
	65	31;—	4		
	60	31;9.5	6 (after 2nd therapy)	65	31;—
9. E. O.	79	8;0	2	90	11;1
10. B. H.	81	28;6	3	100	7;—
	91	21;—	4		
11. E. J.	33	66;3	3	63	24;1
	35	62;6	4		
12. I. M.	91	15;4	4	75	—;—

TABLE 1.—(*Continued*)

	Post-Therapy Tracer			*Pre-Therapy Tracer*	
Patient	*24-hr. Uptake* (%)	*48-hr. Urinary Excretion Days, 1; 2* (%)	*Interval Between Therapy & Tracer (months)*	*24-hr. Uptake* (%)	*48-hr. Urinary Excretion Days, 1; 2* (%)
		B. Euthyroid Clinically			
1. E. R.	50	49.5;4.5	3	66	37;0
2. F. D.	40	30.5;7.5	36	—	—;—
3. P. F.	17	93(1+2)	3	73	7;0.5
	56	47;7	12		
4. A. F.	67	31;2	21	—	1;0
5. L. T.	5	78;17	4	85	23;0
	6	84.5;19	5		
	12	51;18	8		
6. E. F.	20	46;13	2	114	2;1
7. E. O.	11	66;16	13 (after 2nd therapy)	79	8;0
	14	54;18	18 (after 2nd therapy)		
	17	64;11.5	24 (after 2nd therapy)		
8. W. N.	37	54.5;11	15	63	16;2
9. A. P.	21	—;—	5	70	30;3
	23	51;11	8		
10. N. H.	45	15;10	5	54	25;7
11. E. M.	12	66;5.5	2	106	1;0
12. O. M.	39	59;7	16	85	22.5;4
13. D. K.	46	59;3	10 (after 2nd therapy)	65	—;—
14. M. D.	19	70;3	4	114	2.5;2.5
15. L. A.	23	30;7	8 (after 2nd therapy)	57	52;0
	26	29;10	9 (after 2nd therapy)		
	56	54(1+2)	12(after 2nd therapy)		
16. M. M.	40	26;2	4	112	7;0
17. E. B.	26	39;9	3	92	14;0
18. M. B.	31	57;2	6 (after 2nd therapy)	78	18;—
19. F. B.	50	51.5;0.5	4 (after 3rd therapy)	65	38;10
20. J. F.	46	48;3.5	5	92	27;6
21. R. C.	26	53;3	12	72	34;4.5
22. J. Y.	27	67;—	17 (after 2nd therapy)	54	30;2
23. I. H.	32	43;3	3 (after 2nd therapy)	68	30;3
24. L. B.	35	—;3	3	53	47;4
25. M. C.	11	67;17	2½	98	17;1
26. C. H.	34	39;9	5	58	28;3
27. E. M.	17	57;12	3	101	17;2
28. E. S.	41	70;15	10	83	20;4
29. C. B.	56	43;3	3	83	3;0
30. B. H.	34	—;—	2 (after 2nd therapy)	91	21;—
31. A. H.	62	41.5;4	3	87	28;0
	37	—;—	12		
		C. Myxedematous Clinically			
1. C. W.	6	74;10	5	77	32(1+2)
2. F. D.	27	54.5;19	48	—	—;—

— = Data are not available

the pre-therapy 48-hour excretion value. The excretion values were in the normal range in 6 instances, in the borderline range in 2, and were incomplete in 3 tests. It is concluded that in this group only 9 of 18 tracer tests showed the uptake-excretion pattern expected in thyrotoxic patients.

Forty tracer studies were performed on 31 patients listed in Group B. The 24-hour uptake in 22 of these studies was consistent with the usual euthyroid range. In 2 instances it was in the thyrotoxic range, in 5 the uptake was borderline high and in 11 tests the uptake was that which we have seen only in myxedema patients or in patients who have recently taken some iodine-containing medication. The latter would presumably interfere with the uptake of iodide by the thyroid. No such history of ingestion could be elicited in any instance.

The 48-hour excretion data showed that in 15 of 36 tracer studies the excretion values were consistent with a euthyroid state. In 5 tests the values were borderline, in 6 the values were in the thyrotoxic range and in 10 tests the values were in the myxedema range.

In summary, 9 of 36 studies demonstrated the expected uptake-excretion pattern of the euthyroid patient, while 11 studies were more consistent with myxedema or chemical block than with any other interpretation.

In Group C, 2 tracer studies were performed on 2 patients who were myxedematous. Uptake and excretion patterns in both were comparable to what is often seen in the myxedematous subject.

Discussion. These data, according to the ranges stated under *Method*, would indicate that a high 24-hour uptake of I_{131} by a patient following radioiodine therapy for thyrotoxicosis suggests persistence of the thyrotoxicosis. A low 24-hour uptake suggests that the patient is not thyrotoxic, and a normal 24-hour uptake value cannot be interpreted. Apparently the 24-hour determination is a more accurate index of over-all thyroid function in these patients than is the determination of the 48-hour urine excretion of I_{131}.

Physiologists have shown that the thyroid gland performs independent functions that can be studied in the semi-isolated state. The thyroid will accumulate iodide, will synthesize an iodine-containing hormone and will discharge that hormone from the gland into the circulation. The radioiodine tracer test used in this study is essentially a measure of the iodide-accumulating function of the thyroid gland. Keating and associates[6] summarized an experience that suggested a close correlation between thyroid iodide-accumulating function and the function of the thyroid as determined clinically. The report by Soley and associates[8] indicated that this close correlation might not hold in patients who had received therapy to depress over-all thyroid function. Belton and Ross[1] also discussed this problem of the correlation of the tracer test with the clinical status in thyrotoxic patients and concluded that a patient's thyroid might have a reduced iodine storage capacity following treatment for thyrotoxicosis. This reduced capacity, in turn, could allow the iodide-accumulating function of the thyroid to be influenced more readily by extra-thyroidal iodide stores. These extra-thyroidal stores are essentially controlled by the rate of ingestion of iodide and by the rate of utilization of thyroid hormone.

The present data are not readily explained. The rate of ingestion of iodide by a radioiodine-treated, originally thyrotoxic patient who is euthyroid is probably not significantly different from that of his naturally occurring euthyroid counterpart. However,

there is no reason to assume that the rate of peripheral utilization of thyroid hormone in these two types of patients is the same or that the thyroid iodine storage capacities are similar. The effects of treatment on the iodide-accumulating function of the hyperactive thyroid noted in this study could be the result of a therapy-induced alteration in the peripheral utilization of thyroid hormone, so that a little hormone goes a long way and so that hormone production occurs at a slower rate than in the normal subject. Or the alteration could be entirely within the thyroid as suggested by Belton and Ross[1]. Consideration of two other facts suggests that the mechanism is thyroidal, not peripheral. First, there is a fairly good correlation between serum protein-bound iodine concentration and clinical status in all euthyroid subjects, regardless of prior thyrotoxicosis and subsequent treatment[1]. Second, it is well known that the correlation between the thyroidal iodine-accumulating mechanism and the clinical status in the thyrotoxic patient made euthyroid by anti-thyroid drugs is not the same as in the naturally occurring euthyroid subject. It would be interesting to know the results of such a study as the present one in thyrotoxic patients treated surgically.

The two problems noted in the first sentence of this paper can now be considered in terms of the data presented above. In regard to choice of patients for radioiodine therapy, multinodular toxic goiter has not been treated with radioiodine by most clinicians because of early reports stating that excessive doses of radioiodine were needed to produce the desired remission. Perhaps these reported doses merely reflect in part the decreased iodide-accumulating capacity of the irradiated thyroid soon after radioiodine treatment. The actual amounts of isotope delivered to the thyroid may not be excessive. In regard to the second problem, certainly the results in Table 1 demonstrate that the tracer test is a diagnostic aid in following the course of the radiation-treated thyrotoxic subject only when the uptake is elevated.

Summary. 1. The radioiodine tracer test cannot be interpreted in the usual way in the evaluation of thyroid function in a patient recently treated with radioiodine for thyrotoxicosis.

2. The above statement probably reflects an alteration of thyroid iodine storage capacity produced by the treatment.

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THE PATTERN OF HEPATIC DYSFUNCTION IN MALARIA

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Previous clinical studies have shown that in certain systemic diseases consistent patterns of abnormal hepatic function are seen[44,45]. In sarcoidosis[44], rheumatoid arthritis[45], lupus erythematosus[45] and subacute bacterial endocarditis[45], for example, there is a greater degree and incidence of abnormality of the flocculation tests than of dye excretion. It has been suggested that this variety of apparent hepatic dysfunction reflects disturbance of the plasma protein pattern rather than true hepatic abnormality[39,44], although a similar pattern is seen in late convalescent infectious mononucleosis[37] and hepatitis[45]. The hepatic dysfunction reported in malaria has been considered by most observers to indicate parenchymal damage. Although the abnormality has been demonstrated by a number of different tests in naturally acquired and therapeutic malaria[2,4,5,8,9,11,12,15,19-22,25,29,31,33,34,40-42], no consistent pattern of dysfunction has been emphasized. The pattern of apparent impairment of liver function during convalescence from malaria suggests that here also the aberration may be related to disturbance of plasma proteins.

Material and Methods. Seventy-five veterans with malaria, recently returned from Korea, in whose peripheral blood *Plasmodium vivax* was demonstrated, were studied. Clinical data on 25 of these patients have been previously reported[13]. Patients in whom there was evidence of alcoholism, cirrhosis, or infectious hepatitis were excluded from this study. The majority of the patients were between the ages of 20 and 25, with a few above the age of 25 and a small group in the fourth decade. Treatment consisted of standard doses of chloroquine in 47 patients, while the remaining 28 were treated with a combination of quinine and pentaquin as previously described[13]. Most of the patients stated that they had taken chloroquine regularly once weekly while stationed in Korea. Only three reported having had malaria while there.

The tests of liver function included the measurement of bromsulfalein excretion by the method of Mateer and his associates[30], the thymol turbidity by the procedure of Maclagan[27] as modified by Shank and Hoagland[38], and the cephalin-cholesterol flocculation by Hanger's method[14], with the modification of Neefe and Reinhold[32]. The upper limits of normal for these procedures in our laboratories have been 4% retention in 45 minutes, 4 units and a 2 plus reading at 48 hours respectively. In a smaller number of

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patients the zinc sulfate turbidity of Kunkel[23], the 2-hour urine urobilinogen by the method of Schwartz and his associates[43], and the serum bilirubin by the procedure of Ducci and Watson[7] were performed. The upper limits of normal for these have been 12 units, 1 Ehrlich unit, and 1 mg. total bilirubin with 0.2 mg. 1-minute bilirubin, respectively. The level of the total serum proteins and the albumin and globulin fractions were determined by the method of Howe[16]. Albumin levels below 4 gm. per 100 cc. and globulin levels above 3 gm. per 100 cc. were considered abnormal.

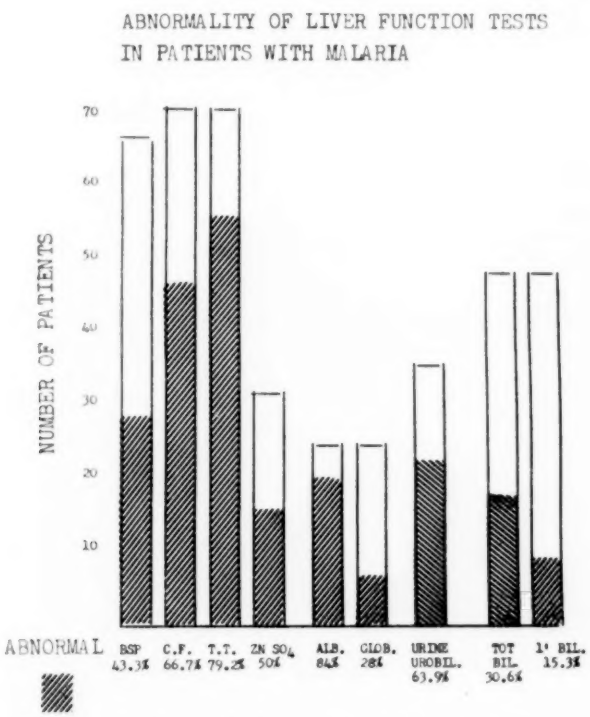

Fig. 1.—Incidence of abnormality of hepatic function.

Results. The excretion of bromsulfalein was abnormal in 43.3% of the patients at some time during the course of their illness. The thymol turbidity and cephalin flocculation tests were or became abnormal in four-fifths and two-thirds of the group respectively (Fig. 1). The range of abnormality of these tests may be seen in scattergrams (Figs. 2, 3, 4). Abnormally high urine urobilinogen excretion was found in 65% of 36 patients studied. The levels were slightly or moderately increased in most patients although in several the increase in excretion was marked with a level of 30 E. U. per 2-hour specimen in one patient. Elevation of the total serum bilirubin was found in approximately one-third of the 59 patients in whom this procedure was done, but the highest level seen was only 1.8 mg. per 100 cc. The "1-minute" bilirubin level, however, was abnormal in only 15%, with the highest value 0.5 mg. per 100 cc. Visible jaundice was not present in any of the patients. Abnormally high gamma globulin levels, as

measured by the zinc sulfate turbidity test, were found in 50% of the 32 patients studied. The highest value obtained with this procedure was 40 Kunkel units. In 25 patients the level of the total serum proteins was measured. Depression of the serum albumin level was found in 84%, while elevation of the serum globulin was observed in 28% of this group. The

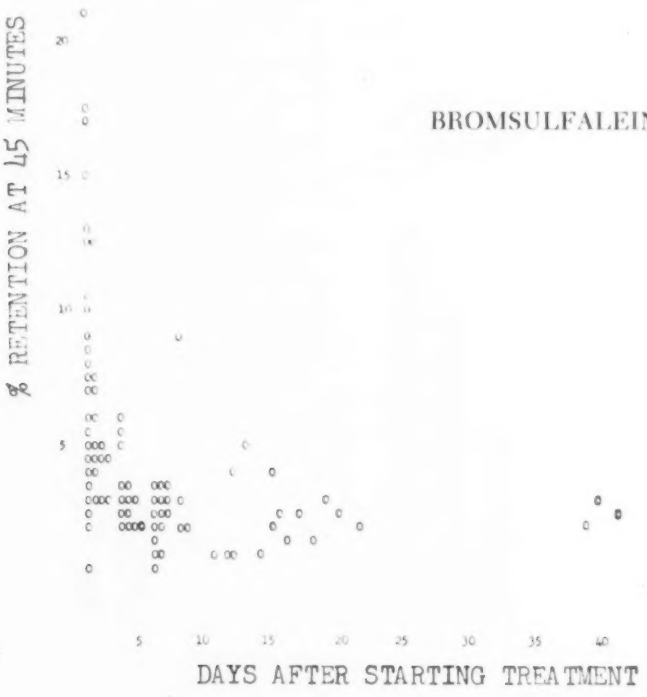

Fig. 2.—Scattergram showing incidence and degree of abnormality of bromsulfalein excretion after initiation of therapy.

levels of the serum albumin were between 3 and 4 gm. per 100 cc. in the majority of patients, with the lowest 2.8 gm., while globulin elevation as high as 4.6 gm. per 100 cc. were observed.

During the first 48 hours after the initiation of therapy, bromsulfalein excretion was frequently abnormal, although for the most part only mildly disturbed (Fig. 2). By the third day almost all of the patients showed a return of this function to normal and thereafter only two values were elevated. Although abnormality of the dye excretion was more frequent than of the flocculation tests during the first 2 days in the hospital, thereafter the pattern changed (Figs. 3, 4). In a number of patients initially normal flocculation tests were replaced by distinctly abnormal ones. Moreover, return of these to normal was frequently delayed for several weeks. Thus, after the third day and until return of liver function to normal, a pattern characterized by normal dye excretion but abnormal flocculation tests was consistently seen. Data available in 27 patients revealed that the longer the

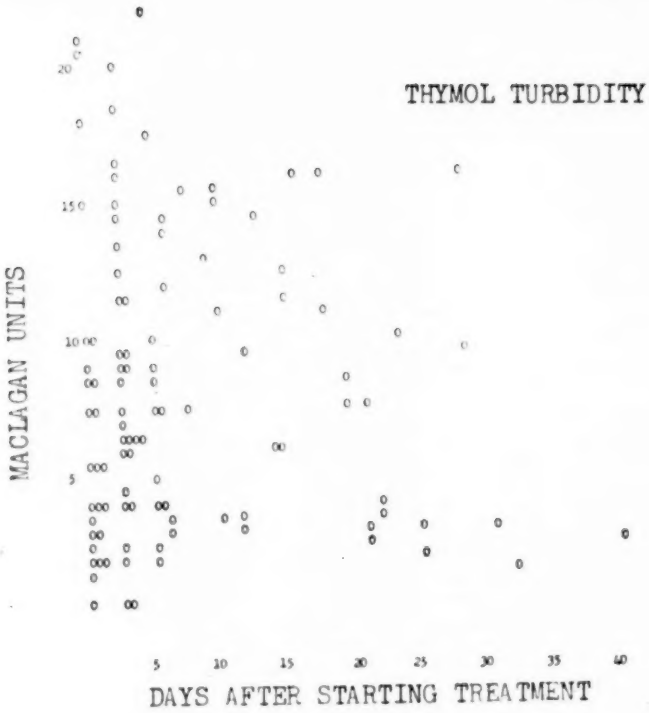

Fig. 3.—Scattergram showing incidence of abnormality of thymol turbidity after initiation of therapy.

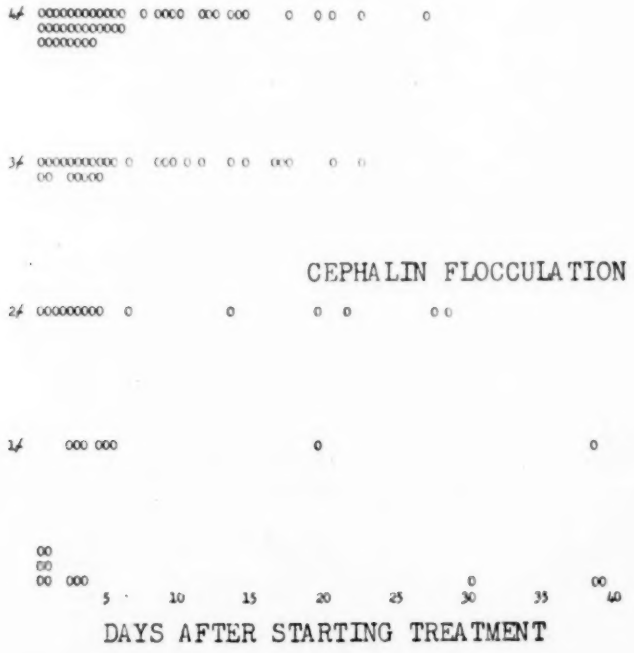

Fig. 4.—Scattergram showing incidence of abnormality of cephalin flocculation after initiation of treatment.

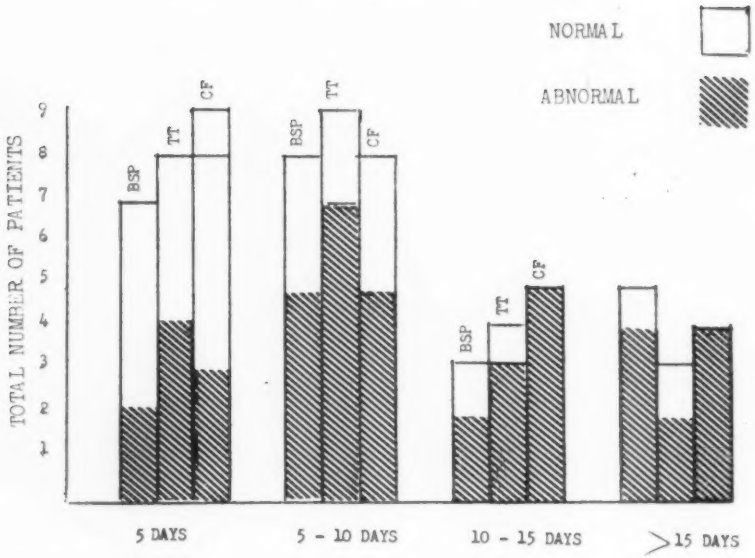

Fig. 5.—Relation of abnormality of liver function to duration of disease as manifested by symptoms.

CORRELATION BETWEEN ZINC SULFATE TURBIDITY AND THYMOL TURBIDITY AND CEPHALIN FLOCCULATION TESTS

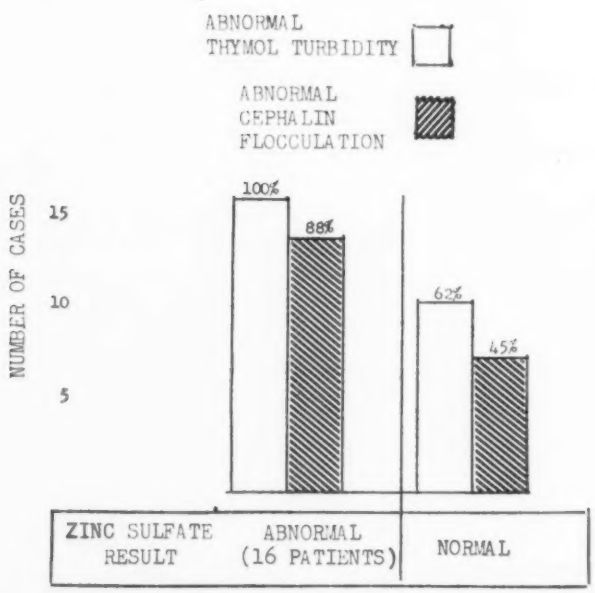

Fig. 6.—Correlation between zinc sulfate turbidity and thymol turbidity and cephalin flocculation tests.

duration of clinically manifest disease before treatment the higher the incidence of hepatic dysfunction (Fig. 5). It was almost twice as great in patients untreated for more than 10 days after the onset of symptoms as in those hospitalized earlier in their disease.

In Fig. 6 is shown the correlation between the three flocculation tests used. Abnormality of the zinc sulfate turbidity was present in 50% of 32 patients. When this test was abnormal, the thymol turbidity was invariably and the cephalin flocculation almost invariably abnormal also. On the other hand, abnormality of the thymol turbidity occurred in 62%, and of the cephalin flocculation in 45%, of the patients whose zinc sulfate turbidity was normal. Thus, of these three flocculation tests, abnormal results were obtained most frequently with the thymol turbidity and least frequently with the zinc sulfate turbidity test.

Discussion. The results obtained in this study are in general agreement with those reported by others[2,4,5,8,9,11,12,15,19-22,25,29,31,33,34,40-42]. The abnormality of hepatic function occurring in the majority of patients can be demonstrated with a variety of tests (Table 1). Most frequently abnormal are the flocculation tests, particularly during convalescence. The transient nature of the early impairment of dye excretion has been emphasized by Machella[26] who has related the inability to excrete bromsulfalein during the acute phase to the effect of fever on this hepatic function. Impaired flocculation tests,

TABLE 1.—REPORTED FREQUENCY OF ABNORMALITY

Liver Function	*Review of Literature*	*Present Study*	*Comment and References*
Bilirubin metabolism Serum bilirubin Icterus index	20%[25]–92%[2]	30% Total	Usually mild elevation during acute phase. Only minimal elevation of direct (1 minute) bilirubin reported in most studies[2,8,9,19,21,25,33,42]. Rare clinical jaundice[5,15,34]. No permanent abnormality[2,41].
Urine Urobilinogen	20%[25]–96%[12]	64%	Elevation during acute phase promptly returning to normal after therapy[4,9,21,25].
BSP excretion	1%[25]–100%[21]	43%	Wide variations of reported abnormalities explained by time of test: A high incidence of abnormality present during febrile phase[21,25], and very low incidence during convalescence[21,22,41].
Galactose tolerance	3%[25]		During acute phase.
Plasma Proteins			Frequency of abnormalities of these tests depends on phase of disease. Abnormality may increase during convalescence and remain elevated for several weeks. Although Keys[21] reported rise of T. T. during course of disease, it did not exceed the upper limits of normal. Electrophoretic studies show hypoalbuminemia, hypergammaglobulinemia, and elevated alpha$_2$- and beta-globulins[11,21,40]. These changes are reflected by abnormal flocculation tests.
Cephalin flocculation	25[25] to 100%[29,31]	66%	
Thymol turbidity	0[21] to 100%[39].	79%	
Albumin	frequently depressed[12]	84%	
Globulin	usually slight elevation[11,21,40].	28%	
Hippuric acid synthesis	23[25] to 52%[32]		During acute phase.
Cholesterol and cholesterol esters	Normal[25] to mild diminution[19,22].		During acute phase.

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however, cannot be so clearly related to the febrile phase, since in many instances the thymol turbidity and cephalin flocculation tests remained abnormal long after apparent return of the patient to well-being and of dye excretion to normal.

It has been suggested by O'Leary and his associates[33], Kopp and Solomon[22], Fredericks and Hoffbauer[8], Glenn and his coworkers[9] and by others[21,31,40,42] that abnormality of hepatic function in malaria is related to parenchymal liver damage. This opinion is supported by the frequency of hepatomegaly[5,20,34] and by reports of histologic abnormality of the liver in this disease[6,9,17,42]. The pathogenesis of these changes has been recently studied by Maegraith and his coworkers[28]. They have suggested that impairment of function and histologic changes result from centrolobular anoxia due to constriction of the hepatic venous tree and associated stagnation of sinusoidal flow. Decreased hepatic blood flow, these workers believe, is the result of fever. Bragdon[3], however, has suggested that parenchymal hepatic damage may result from the effect of heat on the liver cell independent of changes in blood flow. Kaufman and his associates[18] have demonstrated impaired bromsulfalein excretion in patients following inhalation of 10% oxygen. This is an agreement with Rich[35], who has suggested that the impaired hepatic function in hemolytic anemia is incident to the decreased oxygen-carrying capacity of the anemic blood.

It has been shown, however, that even severe anemia does not necessarily impair hepatic function[10,36,45]. Furthermore, impairment of excretion of bromsulfalein may be a reflection of decreased delivery of the dye to the hepatic cell because of decreased blood flow and not necessarily a reflection of parenchymal damage. Irrespective of the basis for the impaired excretion of bromsulfalein, its transient character suggests that the responsible mechanisms must also be briefly present.

Conversely the persistence of abnormality of the flocculation tests suggests a possible relationship to other factors, particularly the plasma proteins, alteration of which occurs in hepatic and extrahepatic disease. A common denominator of this group of diseases including malaria is elevation of the serum globulin. Increase in the gamma globulin[11,21,40] fraction has been reported by others and is reflected by the 50% incidence of an elevated zinc sulfate turbidity in this study. The abnormality of this test and of the cephalin flocculation, however, depend not only on gamma globulin elevation but on albumin depression as well[1]. Thus both tests seem to reflect the relative levels of albumin and gamma globulin, rather than the globulin deviation alone. The frequent hypoalbuminemia and the high incidence of abnormal flocculation tests in malaria are in keeping with this concept. The thymol turbidity test, however, is related to the level of both the gamma and beta globulins[1,24]. As in the case of the zinc sulfate turbidity and cephalin flocculation tests, the degree of abnormality with this procedure may also be lowered by serum albumin[1].

Thus the apparent hepatic dysfunction of malaria seems to have two components. Disturbance of the parenchymal cells is suggested by abnormality of dye excretion, hippuric acid synthesis and alteration of the total and esterified serum cholesterol. The abnormality of the flocculation tests, which is prominent during convalescence, seems also related, as indicated above, to disturbance of plasma proteins as well as to hepatic dysfunction. While hypoalbuminemia is a reflection of hepatic parenchymal dysfunction, hypergamma-

globulinemia is probably related to reticuloendothelial activity.

The relationship of disturbance of bilirubin metabolism in malaria to hepatic function is likewise not well established. It is of interest that only 30% of the patients in this study had hyperbilirubinemia. In few patients, however, was the direct serum bilirubin elevated, and even in these patients the levels were low. Excess urine urobilinogen, however, occurred about twice as frequently. To what extent these abnormalities are a reflection of hemolysis, parenchymal dysfunction, or both, cannot be evaluated from the available data.

Comparison of hepatic function during convalescence in those patients treated with the quinine-pentaquin combination and in those treated only with chloroquine showed no difference. One patient treated with quinine and pentaquin developed a febrile episode and rash 6 days after the initiation of therapy. In spite of this serum sickness-like illness, the hepatic function was no more intensely impaired than in the remainder of the group studied.

Summary and Conclusions. Hepatic function was studied in 75 veterans of the Korean War with malaria due to *Plasmodium vivax*. The flocculation tests were most frequently abnormal. During the acute febrile period a high percentage of patients showed abnormality of function by all tests used. During convalescence, however, disproportionate abnormality of the flocculation tests was noted. It seems probable that this disproportionate abnormality is related in part to plasma protein disturbance and not completely to hepatic dysfunction.

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HYPERTENSION TREATED BY NEPHRECTOMY: A REPORT OF 4 ADDITIONAL CASES AND A RE-EVALUATION OF PROGNOSIS AND CRITERIA FOR OPERATION*

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Recent experience with 4 children whose hypertension was relieved by unilateral nephrectomy led us to survey similar cases reported in the literature. We found an attitude of gloominess pervading most discussions of prognosis and highly unrealistic criteria for determining eligibility for nephrectomy. Sensenbach[14], in 1944, set the pessimistic tone by estimating that but 5 of the 75 cases reported to that time had been cured, and concluded that "the case in which nephrectomy is indicated is rare." Chasis[3], in Brenneman's Practice of Pediatrics writes, "Review of the evidence at hand indicates that a primary renal mechanism can be accepted . . . only with rare exception in unilateral renal disease. One point in this evidence is the failure of unilateral nephrectomy to cure hypertensive disease in children and adults in 69 of the 76 published cases".

It is true that several recent communications have indicated that the outlook is by no means as unfavorable as this. Yet these early conclusions are still repeated or paraphrased, and resistance to the operation is even now encountered in fairly sophisticated medical circles. We felt, therefore, that a re-evaluation of prognosis and of some of the factors which influence prognosis would have virtue at this time.

Nephrectomy for hypertension was carried out in the following 4 instances:

Case Reports. case 1. L. F., a white female, was 10 years of age when she came under our observation in August, 1950.

Family History. An uncle died of chronic nephritis at the age of 20 years. Her mother had had severe pyelitis of pregnancy. There was no history of rheumatic fever.

Past History. Birth and developmental history was normal until the age of 5 years. She had measles, pertussis and severely infected chickenpox.

Present Illness. From 5 to 10 years of age, she suffered 4 attacks diagnosed rheumatic fever, with fever and pains in many joints but no actual swelling and redness of the joints. Following her last attack she was admitted to a convalescent home, where she was found to be a thin, sallow girl appearing chronically ill. The heart appeared normal and the only positive finding was a persistent hypertension of 160/120. Review of her history, in view of this finding, revealed that the patient for the past 3 years had exhibited lassitude, pallor, anorexia and failure to gain weight. Headaches and dizzy spells had been present for 2 to 3 months, nocturia for 3 years, but there was no frequency or hematuria. The urine had never been examined. She was transferred to the Sinai Hospital of Baltimore in September, 1950, for further study.

Physical examination revealed hypertension, early arteriovenous nicking in the fundi, undernutrition and underdevelopment.

Laboratory Studies. The blood showed hemoglobin 14.0 gm.; 7800 leukocytes. The

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urinalyses showed albumin, 0 to trace; rare leukocyte; no erythrocytes; occasional cast. Urine culture gave a growth of *Hemolytic Staphylococcus aureus*. Phenolsulfonphthalein excretion was 80% in 2 hours. Dilution-concentration test showed urinary specific gravities ranging from 1.001 to 1.018. The blood urea nitrogen was 25 mg. per 100 cc. Intravenous and retrograde pyelography showed a small left kidney, rotated, the upper calyx blunted and pear-shaped. There was mild right hydronephrosis. Differential kidney studies gave these results: The urine from the left kidney showed a trace of albumin and 5 to 10 leukocytes per low power field; that from the right kidney was negative. Phenolsulfonphthalein test revealed delayed appearance time and approximately one-half excretion of dye on left compared to right.

Course. She was discharged from the hospital on aureomycin in an attempt to control the urinary infection. Five weeks later the flora had changed to *Proteus*, and Gantrisin was given. She was readmitted in January, 1951; there was no essential change in findings.

Operation. On March 5, 1951, her left kidney was removed.

Postoperative Course. Her blood pressure did not begin to fall for 3 days, but thereafter it fell steadily and rapidly to normal by the 7th day. Readings were 110/70 on the day of discharge, the 20th postoperative day. Blood urea nitrogen on this day was 64 mg. per 100 cc. One month after operation her blood pressure was 90/55. She had gained 5 pounds, had no more headaches or dizzy spells, and seemed "like a new girl" to her parents. The urine was clear. One year after operation her blood pressure was 108/62, and all examinations were normal.

Pathological Report. The removed kidney weighed 28 gm., measured 6.7 by 3.0 by 1.8 cm. The capsule was adherent to the posterior upper pole. Grayish foci and streaks were observed on the reddish brown surface. There was nodular projection at the upper pole. The upper calyx was dilated and hemorrhagic. The cortex of the upper pole was thin, and there was a deeply depressed scar in the lower pole. Microscopic examination showed chronic pyelonephritis in all its various stages, with many hyalinized and thick-walled arterioles throughout the scarred areas.

CASE 2. B. R., a 10-year-old white girl, was admitted to the Harriet Lane Home on the service of Dr. Harriet Guild on 10 November 1952, with the complaint of high blood pressure. The family history was not remarkable. The patient's past history was negative.

Present Illness. Two years prior to admission, urinary frequency was first noted. Eighteen months ago she began to have moderately severe headaches recurring at monthly and then weekly intervals. The headaches increased in severity and frequency until the time of admission to the hospital. There was no past history of any abnormal urinary findings and there was no record of when the high blood pressure was first noted.

Physical examination revealed a lean but otherwise normally developed girl. Blood pressure was 220/160. Visualization of the eye grounds showed slight blurring of both discs, with superficial exudate present on the right and a small hemorrhage on the left. The retinal vessels were narrowed and irregular and there was retinal edema about both optic discs. Examination of the heart revealed a very forceful apical impulse with accentuation of the aortic second sound. Femoral pulsations were present and the remainder of the examination was essentially negative.

Laboratory Studies: The urine showed a specific gravity ranging from 1.010 to 1.018, with a transient trace of albumin. No cells or casts were present and the urine culture was negative. Blood nonprotein nitrogen was 29 mg. per 100 cc. Phenolsulfonphthalein test showed 70% excretion in 2 hours. Intravenous pyelography showed bilateral excretion of the dye, but there was a suggestion of hypoplasia of the left kidney. Retrograde dye examination revealed a very tiny left ureter and a small left kidney. Differential 'phthalein excretion test yielded 35% from the right kidney and no excretion from the left kidney.

Biopsy of skin and muscle of the right calf was performed and in both skin and muscle thicked-walled arteries were found with an appearance characteristic of arteriosclerosis.

On 26 November 1952, operation was performed for the removal of the left kidney. This was found to be very small and aplastic. It measured 4 by 2 by 1 cm. The surface of the kidney was smooth and on cut section revealed very little functioning cortical substance. Microscopic examination showed a varied pattern. Some glomeruli and tubules appeared normal while there were other areas with much scarring and fibrosis. There was, in addition, considerable thickening of the pre-arterioles. The anatomical diagnosis was congenital hypoplasia of the left kidney with arteriolosclerosis.

Immediately following operation the blood pressure fell to a range of 130/90 to 160/120. Within 2 weeks the systolic pressure rarely exceeded 120 to 130 and the diastolic level

was between 70 and 80. Re-examination of the eye grounds at this time showed marked improvement.

She was seen again 7 months after operation. There were no complaints. The blood pressure was 105/60. The eye grounds were completely normal. Urinalysis showed a specific gravity ranging from 1.010 to 1.021 with no albumin and a negative sediment. The phenolsulfonphthalein test showed 80% excretion in 2 hours.

CASE 3. J. D., a 5-year-old Negro boy, was admitted to the Harriet Lane Home on 27 March 1953, with a generalized convulsion. The family history was essentially negative.

Past History. He was entirely well until 22 months of age when he was first hospitalized with pneumonia. During the course of this illness, he developed paralysis of his right arm and leg, the cause of which was not known. His blood pressure was not recorded at that time, and he was discharged home with some residual weakness of the right side.

Present Illness. At 5 years of age he had his first generalized convulsion which apparently responded to simple sedation. Thereafter he was well and asymptomatic until a second convulsion occurred just prior to admission to the Harriet Lane Home.

Physical examination revealed a well-developed and well-nourished boy in a semicomatose state. His blood pressure was 200/160. The fundi showed increased tortuosity of all vessels with some constriction of terminal arterioles. There was increase in the muscle tone of both the right arm and right leg, with corresponding hyperactive deep reflexes. The remainder of the examination was within normal limits.

Laboratory Studies: The hemogram was normal. Urinalysis showed a trace of albumin in the initial urine specimen, but many subsequent examinations were all within normal limits. Spinal tap gave normal fluid without increase in pressure. Blood analyses showed nonprotein nitrogen, 31 mg. per 100 cc.; sugar, 96 mg. per 100 cc.; CO_2, 30.8 mEq.; calcium, 10.7 mg. per 100 cc.; phosphorus, 4.8 mg. per 100 cc.; chlorides, 106 mEq.; sodium, 139 mEq.; potassium, 3.5 mEq. Two benzodioxane tests resulted in no lowering of the blood pressure.

Intravenous pyelogram showed good concentration and visualization of both kidneys. The calyces and ureters on the left were normal. The superior calyx on the right appeared abnormally large. However, retrograde pyelography showed an essentially normal right upper tract.

Retrograde abdominal aortogram revealed a normal right renal artery. No main left renal artery could be demonstrated. There was, however, good filling of the intrarenal arterial branches of the upper pole of the left kidney. There also appeared to be some retrograde vascular filling of the left kidney from the ureteral artery.

During his stay in the hospital he was continued on moderately heavy sedation. At bed rest his blood pressure was in the range of 160 to 210 systolic over 120 to 180 diastolic.

On 1 May 1953, an exploratory operation of the left kidney region was performed. The entire left kidney was mobilized without difficulty and it appeared grossly normal. In dissection of the pedicle there was discovered a mass 2 cm. in diameter, the lower edge of which lay over and compressed the left main renal artery. This mass as well as the left kidney was removed.

Microscopic examination of the mass demonstrated ganglioneuroma. The left kidney weighed 60 gm. and was of normal shape. The capsule stripped with ease. No gross abnormality was noted in the cortex, medulla, or collecting system. The renal artery was patent. Microscopic examination of the kidney revealed focal atrophy of the tubules, rare hyaline glomeruli and scattered throughout the tissue were hyalinized arterioles.

Following operation there was a rapid decline in blood pressure, reaching a level of 140/100 on the third day. For the next 2 weeks, except for an occasional rise, it continued to fall to a level between 120 to 130/80 to 90. At the time of discharge, 3½ weeks after operation, his blood pressure was 120/80. He was seen in the outpatient department one month later and a pressure of 124/82 was recorded.

CASE 4. D.v.C., an 11-year-old white boy was admitted to the Harriet Lane Home on 22 January 1953, complaining of headaches and known hypertension since the age of 3 years. The family history was noncontributory.

Past History. This is hard to separate from the present illness. Birth and neonate were normal. General health was good.

Present Illness. At one year of age a heart murmur was heard and a thrill later developed. These have persisted without cyanosis or dyspnea. Since the age of 3 years there has been known hypertension with frequent headaches. At the age of 6 years the blood pressure was 180/140, and there was questionable rheumatic fever. At 10 years he was hospitalized with streptococcal septicemia and treated with penicillin for 2 months.

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At that time the urine contained a trace of albumin and an occasional leukocyte and erythrocyte. The nonprotein nitrogen was 48 mg. Since then, the nonprotein nitrogens have always been elevated, 60 to 72 mg. per 100 cc. In spite of this, he has felt well, and has gone to school regularly.

Physical examination revealed a well developed but lean boy. The heart was slightly enlarged to the left, and there was a thrill and a harsh systolic murmur over the entire precordium, maximal in the second and third interspaces near the sternum. The blood pressure was 150/110.

Laboratory Studies. The hemoglobin was 16.8 gm. Erythrocytes numbered 5.91 million; the leukocytes 5400, with a normal differential count. Urinalyses were always negative for albumin, cells and casts. The nonprotein nitrogen was 37, 33, 40 and 34 on four separate determinations. Phenolsulfonphthalein excretion was 45% on 23 January 1953, but 80% when repeated 6 days later. Urine concentrated to 1.027. An intravenous pyelogram showed good concentration of dye in both kidneys, but the left appeared small with small calyces. Retrograde study confirmed this finding. In addition, he was presumed to have a patent interventricular septum.

Operation was performed on 30 January 1953. The removed left kidney was small, and its lower pole depressed and distorted. Microscopic examination revealed chronic pyelonephritis.

His postoperative course was uneventful. the blood pressure fell to 115 to 130/82 to 95 by the time of discharge 11 days after operation. The kidney function tests were as they had peen preoperatively.

Re-examination 6 months after discharge from the hospital showed a weight gain of 5 pounds. He felt fine and joined the children of his age in all their usual activities. The blood pressure was 120/70. The heart was of normal size, the thrill and murmur unchanged. The urine was clear and concentrated to 1.040. Phenolsulfonphthalein excretion was 77.5%. The nonprotein nitrogen was still 40 mg. per 100 cc.

Prognosis in Children. In our first case, decision in favor of operation was made after a cursory review of the literature indicated that prognosis might be considerably better in children than in adults. This appeared likely when one simply separated the age groups in Sabin's[12] collected series. Of his 100 cases, 13 were children. *In every one of these 13, the blood pressure fell considerably after nephrectomy.* In 12 the fall was to normal.

Further search has uncovered 13 more examples. These, together with the 4 described above, bring the total in the pediatric age group to 30. In only 2 did nephrectomy fail to reduce blood pressure considerably. In 20, normotensive levels were achieved shortly after operation and maintained until last determined; in 14, more than 1 year; in 6, less than 1 year. In 8, the blood pressure drops were striking but never reached completely normal levels. (See Fig. 1).

To classify these 8 as failures is unwarranted, for included among them are some spectacular near-successes. One child[17], nephrectomized while in coma, with a blood pressure of 225/125, 2 weeks later was alert and his blood pressure was 140/80. Another[6], with severe headache, cerebral hemorrhage and intense retinitis, a blood pressure of 165 to 200/130 to 140, was apparently well, his retinitis gone, 2 years after operation. His pressure, however, had only fallen to 125/80. Others present equally striking stories.

It is also unfair to intimate that those whose blood pressures have fallen to normal but who have not been followed for 1 year, or 2 years, as Sensenbach[14] demanded, should be included amongst the failures. These should be omitted from the statistical calculation entirely, or counted as successes, with minor reservations. For it is the exception for those who have remained normal for 5 or 6 months later to rise.

Prognosis in Adults. In the course of our search of the literature for children nephrectomized for hypertension, records of 97 adults so treated were discovered. No effort was made to ferret

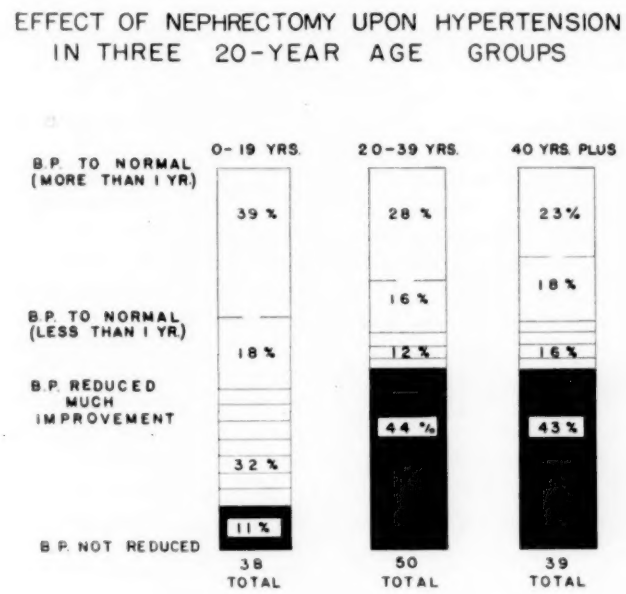

Figure 1.

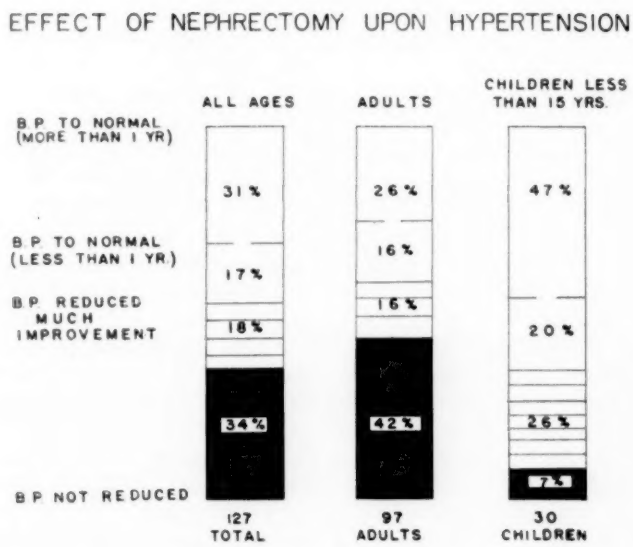

Figure 2.

out every last case reported, nor were large series included whose reports did not include detailed data for each individual case.

Forty-one of the 97 were rendered normotensive by operation, and of these 25 had remained normal for more than 1 year. Another 41 derived no benefit from nephrectomy. The remaining 15 obtained symptomatic relief and reduction of blood pressure, but not to normal levels (See Fig. 1).

Relation of Age to Prognosis. Prognosis in the pediatric age group is therefore considerably more favorable than it is in adulthood.* Does it become worse, stepwise, with advancing years, as most reviewers intimate?

The number of cases is too small to permit of great subdivision. If prognosis worsens with advancing years, the number of failures should be greater in the over-40 year group than in the 20 to 40-year group. This does not appear to be true. Comparing the second and third scores of years, failures comprise 44% and 43% respectively, successes 44% and 41% respectively (See Fig. 2).

The prognostic difference, then, does not appear to depend upon successive increments of age, but may reside in some difference of response between children and adults. Might this not be the same factor which determines the extraordinary superiority of children over adults in the prognosis of acute hemorrhagic nephritis?

Relation of Duration to Prognosis. Langley and Platt[8] are almost the only reviewers to argue that prognosis is not adversely affected by long duration of the disease.

Duration is hard to evaluate because onset is often ill-defined. Recognizing this difficulty, an attempt was made to break down the cases into subgroups, those with estimated durations of 2 years or less, and those of longer durations. In the short-duration group of 45, 67% resulted in success, in the long duration group of 71, 47%. Conversely, failures in the former numbered 23%, in the latter 53%.**

In 22 of the adult cases one can define sharply the onset of the hypertension-producing disease. Operation for stone followed by infection, and various traumata to the kidney were the initiating factors in most. Of 11 whose duration did not exceed 2 years, 9 made complete recoveries and one was an unequivocal failure, whereas in the 11 of longer duration, 3 were cured and 5 were failures.**

Although these differences are not statistically significant, they do suggest that duration may have an inverse relation to excellence of prognosis.

In spite of this, durations of over 5, even 20 years, by no means exclude the possibility of cure. In 5 successful cases, estimated durations were 20 to 23 years[1,5,9,11,15].

Relation of Retinopathy to Prognosis. The presence or absence of eye-ground changes seems to have little bearing upon the ultimate outcome. Disappearance of papilledema, retinal exudate and hemorrhages, and increase in the caliber of retinal arteries have been observed repeatedly to follow nephrectomy.

Langley and Platt[8] tabulated the results of their survey in this regard. Of 25 individuals with normal retinae, 10 were cured; while of 22 with abnormal eye grounds, 14 were rendered normotensive.

Vascular changes in the retina are therefore reversible. That this may be true for arteries of other viscera appears almost certain. Indirect evidence for this assumption was adduced by

*These differences are statistically highly significant. P = less than 0.001.

**These differences are not statistically significant.

Thompson and Smithwick[16] when they found marked arteriolosclerosis in biopsy specimens from the uninvolved kidney of patients who nevertheless became normotensive after removal of the other kidney. Similarly, the presence of arteriolar thickening in the skin and calf muscles of our Case 2 did not preclude cure.

Criteria for Operation. Several sets of criteria have been advanced whereby eligibility for nephrectomy may be determined. Nearly all are open to question[13,14].

1) THOSE STIPULATING A MAXIMUM AGE. Past experience indicates marked superiority in prognosis in the very young, but little difference between the middle years and later years. A score of 7 successes, 3 improvements and 9 failures in 19 individuals, 50 years or over, hardly constitutes a convincing argument against attempting this form of treatment in that age group.

2) THOSE STIPULATING A MAXIMUM DURATION OF THE TOTAL DISEASE PROCESS, OR A MAXIMUM DURATION OF KNOWN HYPERTENSION. While it is possible that successful outcome is rendered less likely by prolonged duration, it must again be stated that there have been too many exceptions to this rule for it to be considered contraindicative. In 7 reported cases with successful outcome, hypertension was known to have been present for more than 3 years, in one of these for 20 years.

3) THOSE REQUIRING THAT DIMINUTION OF FUNCTION MUST HAVE OCCURRED IN THE AFFECTED KIDNEY. Longcope and Winkenwerder[10] and Butler[2] pointed out that hypertension may precede loss of renal function in chronic pyelonephritis. When renal artery constriction was mild, Goldblatt's[7] dogs developed hypertension without demonstrable loss of function. Two cases in this collection had normal intravenous pyelograms, evidence of normal function in one field. More subtle tests of function, such as determination of renal blood flow may be utilized in the future, but at present one must conclude that, from time to time, a kidney whose function appears entirely normal by the usual tests may be extirpated for the relief of hypertension.

4) THOSE STIPULATING THAT TOTAL RENAL FUNCTION MUST BE NORMAL PRIOR TO OPERATION. Good results have been obtained in children when, by the usual tests, function appeared not to be absolutely normal. Maximum urine concentration of 1.017, 2-hour phenolsulfonphthalein excretions of 60% to 65%, blood nonprotein nitrogen values of 40 mg. per 100 cc., and in one instance a urea clearance value of 61% of normal have not precluded successful outcome. Some of the results may represent merely faultily performed tests, but in our Case 4, in whom the nonprotein nitrogen was consistently elevated for 3 years, it is hard to doubt that total renal function was truly diminished.

5) THE STIPULATION THAT RETINOPATHY BE ABSENT AND CHANGES IN CALIBER OF RETINAL ARTERIES MINIMAL. As stated above, all these changes are now known to be reversible.

At present, we cannot predict which patients will be improved by operation and which will not. Tests may be perfected in the future which will supply that answer. Until then hypertensives should be nephrectomized if only one kidney is diseased, or its blood supply compromised, with the expectation that more than one-half the adults and nine-tenths of the children will be cured or greatly improved by the operation.

The only valid contraindications appear to be 1) infection or 2) diminution of function of more than minimal degree of the presumably normal kidney.

Summary. Case histories of 4 children nephrectomized for hypertension have been described. These, together with 26 children and 97 adults reported in the literature, have been analyzed, with prognosis and criteria for operation our chief concern.

One may expect that more than 1/3 of the patients of all ages with unilateral kidney disease will be rendered normotensive by nephrectomy, more than 1/3 will be unimproved, the rest greatly improved.

Children appear to respond to nephrectomy considerably more favorably than do adults. Only 2 of 30 have failed to respond with marked reduction of blood pressure and striking clinical improvement.

Advanced age and long duration of symptoms or of known hypertension are not absolute contraindications to operation.

In our opinion infection of the presumably good kidney, and loss of function of that kidney of more than minimal grade are the only valid contraindications to nephrectomy.

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RAPID BEDSIDE TEST FOR SERUM CHLORIDE AND BICARBONATE

A Further Investigation of Scribner's Method

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The importance of correct diagnosis and treatment in electrolyte-acid-base disturbance has been stressed for many years. Van Slyke's[3] volumetric method for CO_2 determination, and Saifer and Kornblum's[1] dichlorfluorescein method for chloride determination have established the baseline for diagnosis and treatment. However, both methods require elaborate apparatus and the service of a trained biochemist. Scribner[2], in 1950, described a simple, inexpensive bedside method of determining bicarbonate and chloride in serum, which was a distinct forward step.

Scribner's method was employed by the author in a series of 17 cases, the findings of which are here presented in a preliminary report. The results were checked with the Van Slyke and the Saifer and Kornblum methods. The findings of this series were quite similar to those of Scribner, although 19.05% of the 42 comparative tests made for bicarbonate determination were beyond the expected deviation of ± 4 vol.%. Findings with the chloride determination methods of Saifer and Kornblum as well as Scribner showed a chloride deviation within the expected range of ± 2%.

Scribner's Technique. REAGENTS. Standard chloride-carbonate solution: 1.32 gm. dry, reagent grade, anhydrous sodium carbonate and 5.85 gm. pure, dry sodium chloride dissolved in distilled water and diluted to 1 liter.

Standard tenth-normal nitric acid: 7 cc. concentrated nitric acid diluted to 1 liter with distilled water. To standardize, 4 cc. standard chloride-bicarbonate solution, with 1 drop methyl orange added as indicator, are titrated with above made nitric acid, diluting the nitric acid until exactly 1 cc. will react with 4 cc. of standard chloride-bicarbonate solution.

Standard tenth-normal sodium hydroxide: 5 gm. dry sodium hydroxide dissolved in 1 liter distilled water. Sodium hydroxide solution diluted until exactly 0.80 cc. will react with an equal amount of the standard tenth-normal nitric acid in the presence of methyl orange as indicator.

Indicator: 0.4% diphenylcarbazone in 95% ethyl alcohol.

Phenol red color standard: 4.0 mg. phenol red per 100 cc. "p-hydrone" buffer, to be kept in sealed ampule. (If boiled for 30 minutes in ampule, it will keep indefinitely.)

Mercuric nitrate: 17.13 gm. fresh mercuric nitrate dissolved in 100 cc. distilled water. One cubic centimeter of concentrated nitric acid added and made to volume of one liter with distilled water.

SUPPLIES. 6 2-ounce standard medicine dropper bottles with one-piece rubber caps

1 1-ounce bottle as above

4 1-cc. tuberculin syringes

1 4-inch (10 cm.) titrating test tube, 1 inch (2.5 cm.) in diameter

1 3-inch (7.5 cm.) test tube, wide enough to accommodate above tube

Handling of blood sample: 3 cc. blood obtained by venipuncture is placed in dry test tube, stoppered to prevent any contact with air, and allowed to clot. The sample may be centrifuged to obtain more serum.

STANDARDIZATION. Perform bicarbonate titration as directed below, using the standard chloride-bicarbonate solution as sample. If the result is 25 mEq. per liter for the carbonate titration, the method is standardized; if not, the amount of alkali placed in the syringe should be adjusted so that a result of 25 mEq. per liter is obtained. Then titrate the chloride of the standard solution. The method is standardized when 1 cc. of the mercuric nitrate reacts exactly with an equal amount of the standard chloride solution. The method has to be standardized frequently, especially if one of the solutions is renewed.

PROCEDURE. 1. Keep test tube free from traces of mercury.

2. Rinse sample syringe with small amount of serum to be tested.

3. Fill sample syringe with amount of serum determined by standardization described above and deliver into titrating test tube.

4. Fill acid syringe with 0.70 cc. of tenth-normal nitric acid and deliver into titrating test tube.

5. Agitate titrating test tube well for about 30 seconds.

6. Add exactly 5 drops of indicator; fill alkali syringe to exact volume with alkali as determined by standardization, and deliver into titrating test tube drop by drop. As red color of standard is approached, deliver only fractions of a drop at a time, until red color does not fade further.

7. The sodium hydroxide left in the syringe equals the serum bicarbonate in milliequivalents per liter. This figure multiplied by 2.23 will give the result in volumes percent.

8. Add 2 cc. of tenth normal nitric acid.

9. Fill mercuric nitrate syringe to correct setting as determined by standardization and deliver drop by drop into titrating test tube until purple color is approached, then only fractions of a drop at a time until color does not fade further.

10. Each 0.01 cc. mercuric nitrate equals 1 milliequivalent of chloride per liter.

Experiments. a) CHLORIDE STUDIES. Fifty blood samples were examined for chloride content by both Scribner's and the dichlorofluorescein chloride methods. The average deviation of Scribner's method was $\pm$ 0.76% and in no case greater than $\pm$ 2%. In 12 specimens there was no deviation; in 11 specimens, a deviation of $\pm$ 1%; and in 27 specimens, a deviation of $\pm$ 2%. The details are given in Table 1.

b) SODIUM BICARBONATE STUDIES. Forty-two blood samples were examined for bicarbonate by both Scribner's and Van Slyke's volumetric methods. The average deviation of Scribner's method was $\pm$ 3 vol.%. However, in this series 19% of the specimens showed greater deviation from the standard procedure than the $\pm$ 4 vol.% reported in Scribner's initial study. In 6 specimens (14.3%) there was no deviation; in 8 specimens (19%) the deviation was $\pm$ 1%; in 8 specimens (19%), $\pm$ 2%; in 6 specimens (14.3%), $\pm$ 3%; in 6 specimens (14.3%), $\pm$ 4%; and in 8 specimens (19%), more than $\pm$ 4%. Details are given in Table 2.

As Scribner points out, the bedside method is sufficiently accurate and is clinically useful in following the bicarbonate-chloride serum level of patients

as treatment proceeds, as will be shown in 2 cases in which treatment was guided by the findings with this method.

TABLE 1.—CHLORIDE CONTENT (IN MEQ) AS DETERMINED BY 2 METHODS IN 50 BLOOD SAMPLES

Spec.	Scribner	Saifer Kornblum	Deviation %
1	101	99	+2
2	104	102	+2
3	100	100	0
4	102	104	−2
5	99	100	−1
6	103	101	+2
7	85	83	+2
8	84	86	−2
9	109	107	+2
10	100	100	0
11	95	93	+2
12	109	109	0
13	84	82	+2
14	100	98	+2
15	90	88	+2
16	107	105	+2
17	99	99	0
18	82	81	+1
19	103	103	0
20	93	91	+2
21	90	88	+2
22	90	90	0
23	99	100	−1
24	100	100	0
25	95	93	+2
26	97	96	+1
27	100	102	−2
28	88	90	−2
29	100	98	+2
30	100	100	0
31	99	98	+1
32	102	104	−2
33	90	90	0
34	99	98	+1
35	82	84	−2
36	95	96	−1
37	99	100	−1
38	97	98	−1
39	99	97	+2
40	99	97	+2
41	95	93	+2
42	100	100	0
43	93	95	−2
44	100	98	+2
45	100	99	+1
46	96	94	+2
47	100	102	−2
48	100	100	0
49	100	100	0
50	99	100	−1

Case Reports. CASE 1. (See Fig. 1). The patient, a 22-year-old white male, was under observation for flank pain associated with dysuria, anorexia and vomiting of several days' duration. From the age of 12, he had been treated for diabetes, and 33 months prior to his present hospitalization, he was treated for subacute glomerulonephritis. Admission ex-

TABLE 2.—BICARBONATE CONTENT (IN VOL.%) AS DETERMINED BY 2 METHODS IN 42 BLOOD SAMPLES

Spec.	Scribner	Van Slyke	Deviation %
1	47	50	−3
2	35	39	−4
3	47	47	0
4	45	44	+1
5	60	58	+2
6	84	75	+9
7	60	61	+1
8	62	58	+4
9	54	56	−2
10	40	39	+1
11	53	51	+2
12	53	53	0
13	40	32	+8
14	57	55	+2
15	57	54	+3
16	53	53	0
17	53	45	+8
18	35	28	+7
19	55	57	−2
20	51	51	0
21	49	51	−2
22	67	70	−3
23	55	60	−5
24	45	51	+6
25	58	59	−1
26	55	58	−3
27	45	49	−4
28	58	56	+2
29	54	56	−2
30	52	51	+1
31	58	58	0
32	53	49	+4
33	55	59	−4
34	55	54	+1
35	67	74	−7
36	67	70	−3
37	55	55	0
38	42	33	+9
39	38	39	−1
40	45	49	−4
41	60	63	−3
42	49	48	+1

amination showed slight cardiac enlargement and a blood pressure of 90/50. Urinalysis was negative for sugar and acetone but 4 + albumin; the sediment showed many leukocytes and few erythrocytes. The patient was given intravenous fluids. No disturbance of the electrolyte-acid-base, was demonstrable. On the 7th hospital day, the patient became semicomatose, exhibited marked facial as well as generalized edema, and his diabetes be-

came uncontrollable. The urinary output had decreased to 600 cc. in 24 hours, despite administration of 2,000 cc. of Ringer's lactate intravenously. Specimen No. 18 examined on this day revealed 7 vol.% less CO_2 with Scribner's method than was found by the Van Slyke method. At this time the nonprotein nitrogen was 180 mg., blood urea nitrogen 92 mg. and blood sugar 322 mg. per 100 cc. Although the patient slowly responded with increasing alkali reserve and urinary output, the next two blood samples (Nos. 23 and 35) showed a persistently greater deviation from the Van Slyke method: 5 vol.% and 7 vol.%. When the disease entered the chronic stage, the deviation returned within the expected range

CASE 2. (Fig. 2). This figure shows the result of treatment on the serum chloride level in a 64-year-old, white male, who was treated for dry gangrene of the entire right leg, toxic psychosis and chronic alcoholism. The patient refused amputation. His leg was packed in ice, intravenous fluids were administered and antibiotic treatment begun. Because of his critical condition, an exact fluid balance could not be obtained. Close follow-up studies for electrolyte-acid-base disturbance showed continuous chloride loss in the presence of saline infusion theoretically adequate in amount. On the sixth hospital day, oral medication with potassium chloride was started and within 24 hours the serum chloride level returned to normal. On the 21st hospital day, a deviation of the bedside method from the Van Slyke method by + 8 vol.% was noted. The patient expired 3 weeks later with uncontrollable septicemia.

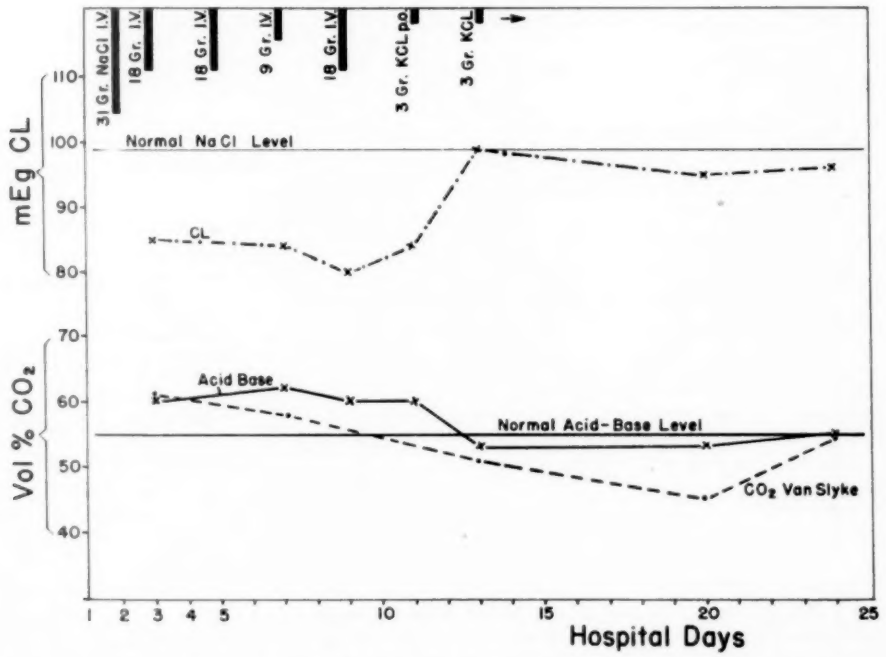

Figure 1 illustrates chloride and CO_2 levels of Case 1, obtained by the bedside method and the Van Slyke method, and response of acidosis to intravenous therapy with calculated amounts of Ringer's lactate. Note the close approximation of the curve obtained by the Van Slyke method and the CO_2 titration by the bedside method.

Comments. As indicated by the comparative findings in Tables 1 and 2, Scribner's method is sufficiently accurate for adequate estimation in electrolyte-acid-base studies. The cases presented above show the method to be very helpful in following the results of treatment, despite its deviation from

the standard laboratory examinations. Experience in using Scribner's procedure will no doubt result in more accurate findings. This simple and inexpensive method is highly recommended as an aid in following progress of treatment where electrolyte-acid-base problems are present. A wider use of this method will simplify the determination of the exact fluid balance.

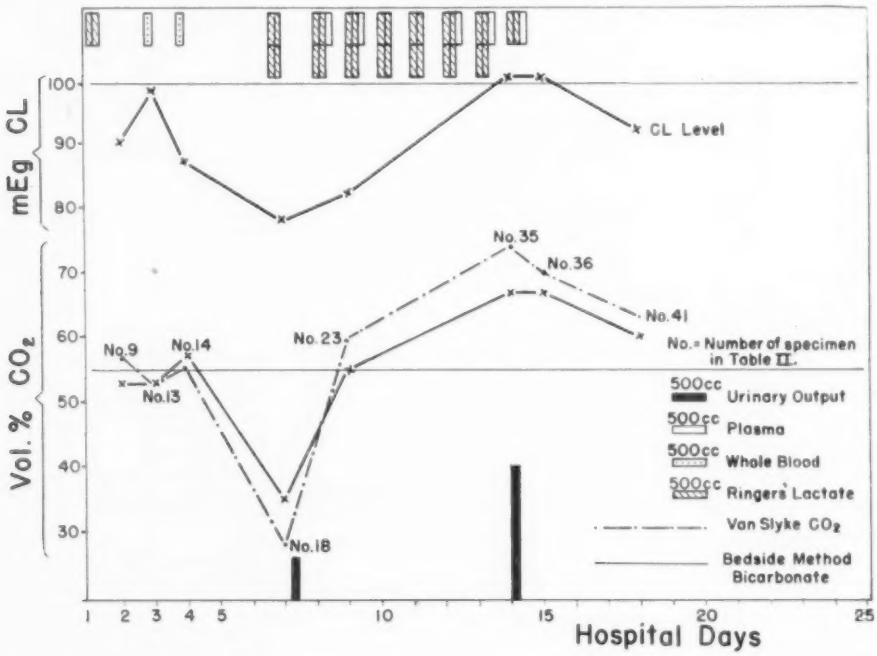

Figure 2 shows the marked response of the serum chlorides to oral KCl therapy in Case 2, after failure of adequate intravenous sodium chloride therapy. This illustrates well how much information can be gained by using the bedside method, when more elaborate methods are not available.

Summary. 1. Determinations of serum chloride with Scribner's bedside method and Saifer and Kornblum's method showed the expected deviation of $\pm 2\%$.

2. Determinations of serum bicarbonate with Scribner's bedside method and Van Slyke's volumetric CO_2 method were found to be within the expected range of deviation of ± 4 vol.% in 81% of the cases.

3. The method offers an inexpensive, simple, accurate bedside procedure for effective control of therapy in cases of electrolyte-acid-base disturbance.

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THE RELATION OF THE SERUM INHIBITOR OF SERUM-EXTRACTED STREPTOLYSIN S TO SERUM PHOSPHOLIPID FROM THE STANDPOINT OF RHEUMATIC FEVER

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There is a growing conviction that the hemolytic streptococcus is the cause of rheumatic fever, presumably acting through some sort of antigen-antibody mechanism. The observations reported herein represent part of an investigation of the possibility that streptolysin S is the streptococcal component which is responsible for rheumatic fever.

Beta hemolytic streptococci of group A produce two hemolysins which Todd[12] has designated streptolysin O, meaning oxygen-labile, and streptolysin S, meaning serum-extractable, which signifies that serum removes the hemolysin from the bacterial cell. Streptolysin O has received more attention and is sometimes referred to simply as streptolysin. It is well known that antibodies capable of inhibiting hemolysis by streptolysin O appear with a high degree of regularity in man following hemolytic streptococcal infection or in animals following streptococcal immunization. On the other hand, there is evidence[6,10,12] that the serum of any individual of the human or other species regardless of previous streptococcal contact is able to inhibit hemolysis by streptolysin S. This is evidently a physico-chemical rather than an antibody effect. The existence of antibodies directed against streptolysin S has not been consistently demonstrable.

Some basic information is available regarding the nature of streptolysin S and the component of serum which inhibits its action. Streptolysin S is highly unstable, deteriorating rapidly at 37° C. In the analyses of Herbert and Todd[4] it resembles a lipoprotein. Hewitt and Todd[5] found that it is inhibited by ovolecithin. Humphrey[7] showed that 60% of the ability of human serum to inhibit streptolysin S is removed by extracting the serum with ether. On the basis of this and other evidence he concluded that the serum inhibitor is likewise a lipoprotein. A general quantitative relationship between S-inhibitor and serum phospholipid was demonstrated by Stollerman, Bernheimer and MacLeod[10] who found that both are high in the dog and low in the rabbit and that the lecithinase produced by *Cl. Welchii* can remove 50 to 83% of the capacity of human serum to inhibit streptolysin S. They concluded that phospholipid, particularly lecithin, is an active component of the serum inhibitor of streptolysin S. Comparing lecithin concentration with the strength of the S-inhibitor in individual human sera, Stollerman, Brodie and Steele[11] showed

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a positive correlation, although within broad limits rather than narrowly linear. Similar observations are reported in the present paper.

Stollerman *et al.*[10,11] used a streptolysin prepared by the method of Bernheimer and Rodbart[1] which depends on the fact that enrichment of the culture medium with nucleic acid permits abundant production of a hemolysin which is spontaneously released from the streptococcal cell in the absence of serum. In most respects this hemolysin appears to be identical with Todd's streptolysin S. However, it is more stable, indicating that the identity is not complete. For this reason we have used a serum-extracted hemolysin rather than one induced by nucleic acid.

Materials and Methods. SERA. The subjects were mostly adults in the wards and dispensaries of the Pennsylvania Hospital, with the addition of a few children in the Children's Hospital of Philadelphia and a few normal adults and normal children. Sera with more than a faint trace of hemolysis were discarded. After the addition of 'Merthiolate' (sodium ethyl mercuri thiosalicylate, Lilly) to a final concentration of 1:10,000, the serum was stored at 4° C. and tested before it was 6 weeks old. Within this interval significant changes were not found in lipid phosphorus or inhibition of streptolysin S. Thereafter there was a gradual increase in S-inhibitor and usually a slow decline in lipid phosphorus. Similar effects of aging on streptolysin S inhibitor have been noted by others[10].

LIPID PHOSPHORUS. The method used was that of Youngburg and Youngburg as described by Hawk, Oser and Summerson[3]. In the early part of the program, analyses were made in duplicate. Since statistical analysis of the differences between duplicate determinations on 115 sera showed a standard error of only $\pm$ 0.247 mg. per 100 cc., the majority of subsequent analyses were single determinations. Inasmuch as phosphorus comprises approximately 4% of the serum phospholipid molecule, serum lipid phosphorus values may be translated to phospholipid by multiplying by 25.

STREPTOLYSIN S. Streptococcal strain Blackmore, which produces only streptolysin S without detectable streptolysin O, was used throughout. The hemolysin was contained in the supernate of a 14 to 16 hour culture in a lightly inoculated medium of the following composition: beef heart for infusion (Difco) 50 gm., proteose peptone (Difco) 20 gm., NaCl 2 gm., Na_2HPO_4 1 gm. and distilled water 1000 cc.; final pH 8.0. This medium was used in tubes containing 5 cc., with the addition of sterile horse serum without preservative to a concentration of 20% by volume. The culture supernate was preserved in 2 to 3 cc. lots either at — 16° C. or by lyophilization. The lyophilized product was stored at — 16° C. The material thus prepared was hemolytic in dilutions up to 1:320 or 1:640 in the absence of additional serum. Hemolytic potency remained essentially unchanged after 2 years' storage in either the frozen or the lyophilized form. These 2 forms of hemolysin appeared to be equally responsive to inhibition by human serum, although minor differences were noted between them upon inhibition by horse serum.

SERUM INHIBITOR OF STREPTOLYSIN S. Because of the instability of the hemolysin, the lack of a stable standard for comparison and the occasional indistinctness of the titration endpoint, this determination is not as satisfactory as the measurement of antistreptolysin O. However, the results of repeat determinations rarely varied by more than one tube and high or low values were obvious and consistently reproducible.

Because of variations in erythrocyte susceptibility, a titration of hemolysin inhibition by a standard human serum diluted 1:12.5 was made as a preliminary to each test, using a modification of the procedure of Rantz and Randall[8] for antistreptolysin O determination. Physiologic salt solution was the diluent throughout. Ten hemolysin dilutions ranging from 1:12.6 to 1:33 were made without blowing out the pipette, thus eliminating a slight inaccuracy. The stock tube of hemolysin was placed in the refrigerator until needed for the second portion of the test. One cc. of the standard serum diluted 1:12.5 was added to 0.5 cc. of each hemolysin dilution and the contents were well mixed by tapping the tubes individually. After incubation for 15 minutes in a water bath at 37° C., each tube received 0.5 cc. of a 2% suspension of human red blood cells, with mixing as before. This preliminary 15-minute bath, for the sake of contact between hemolysin and serum inhibitor, was probably unnecessary, as subsequent experiments have shown that the hemolysin has greater avidity for the inhibitor than it has for the erythrocytes. After

another 45 minutes in the bath, the tubes were swung 4 minutes at approximately 2500 r.p.m. in an angle centrifuge. The first tube with no trace of hemolysis, as read by daylight against white paper on the tabletop, indicated the "combining" dilution of hemolysin.

In the second portion of the test, which followed without delay, each unknown serum was tested in 5 dilutions: 1:6.3, 8.3, 10, 12.5 and 16.6. To 1.0 cc. of each of these dilutions was added 0.5 cc. of the previously determined combining dilution of hemolysin, with the remainder of the procedure as before. Unknown sera were tested up to 12 at a time, accompanied by the standard serum in the same dilutions. The reciprocal of the highest dilution in which hemolysis was completely inhibited was the titer of the serum in units per cc. Evaluation of indistinct endpoints was aided by comparison of the colors in higher serum dilutions with those in other rows. Delay in reading was avoided, as the colors deepened slowly on standing. The standard serum was sometimes one tube above or below the expected value of 12.5 units per cc. When this happened, appropriate corrections were made in the values of the unknowns. Sera with low readings were retested in dilutions of 1:3.2, 4.1 and 5 and those with high readings in dilutions of 1:20 and 25. In the lowest serum dilutions, reading was easier in the absence of postprandial lipemia.

Red blood cells were supplied from random donors once or twice a week by the hospital blood bank, as a mixture of 5 cc. of whole blood and 50 cc. of physiologic salt solution. The cells were washed once on the day of receipt and again just before the test. They were used within 3 days. Standard human serum was obtained throughout from the same individual, being renewed at 6-week intervals. This donor remained free of febrile illness during the period of the experiment. Selected independently on the basis of the availability of the donor, our standard gave results which are generally a little lower than those of Stollerman and his associates[9,11].

TABLE 1.—CHANGES IN LIPID PHOSPHORUS AND STREPTOLYSIN S INHIBITOR WITH POSTPRANDIAL LIPEMIA IN SERA OF 14 HOSPITAL PATIENTS

Before Breakfast			*Same Day—4–5 P.M.*			*Change in*		
Turb units	*LP mg.%*	*S Inhib units*	*Turb units*	*LP mg.%*	*S Inhib units*	*Turb units*	*LP mg.%*	*S Inhib tube*
34	6.7	5	37	6.0	4.1	+3	−0.7	−1
32	8.4	10	36	8.9	10	+4	+0.5	0
30	6.9	4.1	36	6.2	3.2	+6	−0.7	−1
29	9.2	8.3	35	8.4	8.3	+6	−0.8	0
44	5.1	5	55	5.0	4.1	+11	−0.1	−1
38	9.9	6.3	51	11.2	5	+13	+1.3	−1
32	7.9	5	52	9.1	5	+20	+1.2	0
37	10.4	10	68	8.9	8.3	+31	−1.5	−1
26	8.5	10	70	9.3	10	+44	+0.8	0
32	7.4	10	78	9.1	10	+46	+1.7	0
37	9.0	10	85	9.8	8.3	+48	+0.8	−1
38	9.9	10	86	10.8	10	+48	+0.9	0
31	6.9	6.3	81	6.8	5	+50	−0.1	−1
46	12.0	10	135	12.1	8.3	+89	+0.1	−1

Turb = turbidity units measured in Klett colorimeter with filter No. 66. The fasting sera were clear or nearly so. A reading of 85 would correspond roughly with + gross lipemia and one of 135 with ++ on a scale of ++++.

LP = lipid phosphorus.

S Inhib = streptolysin S inhibitor.

Results. It was desirable to learn the extent to which results would be affected by meals containing ordinary amounts of fat. The values in the table show that postprandial lipemia of varying degree is accompanied by tendencies toward a slight decrease in the serum inhibitor of streptolysin S and a slight rise in lipid phosphorus. These trends, however, are inconstant and do not parallel each other or the visible

lipemia. Since the differences are not much more than the experimental error of the methods, it is felt that postprandial sera are acceptable. Others[7,9] have found postprandial lipemia to be without effect on the S-inhibitor.

Lipid phosphorus and streptolysin S inhibitor readings on individual human sera are presented in Fig. 1. It is evident that these values do not bear a linear relationship to each other even though an allowance of one tube in either direction be made for the lack of a high degree of accuracy in the determination of hemolysin inhibitor. However, a rough parallelism is apparent, in the sense that a weak inhibitor was rarely found in the presence of a high lipid phosphorus and with few exceptions a strong inhibitor did not accompany a low lipid phosphorus. Correlation becomes more definite in the region of low readings for both determinations. As lipid phosphorus falls the S-inhibitor tends to grow progressively weaker, an effect which is especially marked when lipid phosphorus is below 6 mg. per 100 cc. Whatever other factors may be concerned in the mechanism of inhibition, a low serum lipid phosphorus appears to be in most instances a prerequisite to a very weak serum inhibitor of streptolysin S. In the opposite direction, a high lipid phosphorus is less consistently accompanied by a strong inhibitor. As examples of hyperphospholipidemia, sera of pregnancy, lactation and nephrosis are included in Fig 1. Of these, only pregnancy was regularly associated with a strong S-inhibitor. No characteristic differences were noted between children and adults with regard to the relation of S-inhibitor to serum phospholipid.

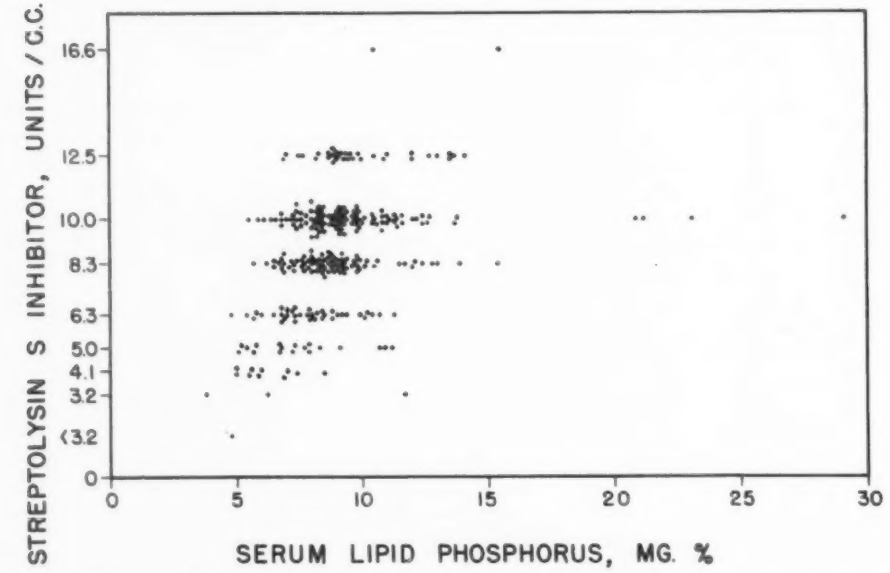

Fig. 1.—Relation of streptolysin S inhibitor to lipid phosphorus in 287 sera from 273 subjects.

Serum lipids are known to be diminished in the presence of fever[2]. This effect accompanies fever of a variety of origins. The mechanism is not known aside from the fact that fever itself is

not responsible. Stollerman and Bernheimer[9] found that the serum inhibitor of streptolysin S is often although not consistently weakened in the presence of fever. Our experience has been similar. Except for a few instances in normal children, most of the S-inhibitor readings below 6.3 units per cc. in the figure occurred in adults with fever above 101° F. The S-inhibitor, however, is not as sensitive to the circumstances accompanying fever as is serum lipid phosphorus. The latter is usually less than 7.5 mg. per 100 cc. when the temperature is over 101° F., whereas a consistent marked fall in S-inhibitor seems to require that the patient be not merely febrile but also seriously sick. For example, S-inhibitor values below 5 units per cc. were found most constantly in the presence of such states as extensive peritonitis or advanced tuberculosis. Serum lipid phosphorus does not fall to the same level in all subjects who have fever of comparable intensity. The point to which it descends presumably depends in part on its normal level before the onset of fever. Likewise, there appear to be individual differences in the degree of depression of S-inhibitor under the influence of fever and illness.

Discussion. The foregoing results are in better agreement with the conclusion of Stollerman, Brodie and Steele[11] that the streptolysin S inhibitor titer falls abruptly with very low concentrations of serum phospholipid than with their conclusion that the two values tend to run parallel at higher phospholipid levels. In comparison with their data, ours show a wider spread of phospholipid in the middle and upper strengths of S-inhibitor, with less tendency for S-inhibitor to level off as phospholipid rises, although fewer pathologically high values are included in the present series. This discrepancy may be due to differences in the method of preparation of streptolysin S. The serum inhibitor of streptolysin S is a complex substance, the details of whose nature, according to Humphrey[7], vary between species and perhaps even among individuals of the same species. Of its components, only phospholipid has so far been identified. Our results suggest that, when the serum-extractable form of hemolysin is used, phospholipid has a quantitative relation to the S-inhibitor only at very low levels, being overshadowed in quantitative importance at higher levels by other factors which are as yet unknown.

The failing strength of streptolysin S inhibitor with decreasing serum phospholipid is of particular interest in connection with rheumatic fever. Evidence recorded elsewhere[13] indicates that serum phospholipid tends to be below average in persons who are susceptible to rheumatic fever. Together with the present observations, this supports the possibility that the production of rheumatic fever may depend on a deficiency in the natural ability of serum to neutralize streptolysin S, which would imply that streptolysin S is the antigenic streptococcal fraction specifically responsible for this disease.

The ability of streptolysin S to stimulate the formation of demonstrable antibodies is controversial but may prove irrelevant to the pathogenesis of rheumatic fever. Streptolysin S deteriorates so rapidly at body temperature that antibodies would probably be aroused not by the intact hemolysin but by its breakdown products. Such antibodies would escape detection by present methods. Inhibition of hemolysis is the only method available for the recognition of antibodies directed against any part of streptolysin S. Since this method can only detect antibodies which react with superficial configurations of the intact hemolysin, antibodies arous-

ed by internal fractions of this substance would pass unrecognized. Streptolysin S therefore cannot be excluded as the cause of rheumatic fever on the ground that its antigenicity is not demonstrable.

Summary. Normal serum contains a non-antibody substance capable of inhibiting the streptococcal hemolysin known as streptolysin S, not to be confused with the more familiar streptolysin O. This inhibitor is a complex whose effectiveness depends in part on phospholipid. Previous observers, using a form of streptolysin S produced by enrichment of the culture medium with nucleic acid, have found that the serum inhibitor bears a roughly quantitative relationship to serum phospholipid, declining abruptly when the latter is very low and levelling off as it rises. The present observations, made with streptolysin S extracted from the bacterial cell by serum in the absence of added nucleic acid, provide confirmation to the extent that a low serum phospholipid is usually a prerequisite to a very weak S-inhibitor. In the middle and upper zones of the normal range of phospholipid the correlation was less definite.

In the light of evidence presented elsewhere to the effect that serum phospholipid tends to be below the normal average in individuals who are susceptible to rheumatic fever, the possibility is discussed that streptolysin S may be the cause of rheumatic fever and that susceptibility to this disease may vary inversely with the strength of the natural serum inhibitor of streptolysin S.

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PROGRESS
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MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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NON-CHROMAFFIN PARAGANGLIOMA IN THE TEMPORAL BONE

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DURING the past 9 years the terms of glomus jugulare tumor, carotid body like tumor and non-chromaffin paraganglioma of the middle ear have been noted with increasing frequency in American and European literature. These terms indicate a rare group of expansive benign tumors in the field of otology which exhibit well-defined clinical manifestations and microscopic characteristics.

Rosenwasser[20], in 1945, described the first case of a carotid body tumor of the middle ear extending into the mastoid, but without demonstrable evidence of a tumor involving the carotid body in the neck. He noted the similarity of its microscopic appearance to the glomus jugulare as described by Guild[8], in 1941, and suggested that the tumor originated from the glomus jugulare.

During the past 9 years there have been reported a total of 75 cases, including 4 of our own now in the process of publication, which are considered reliable from their clinical aspects and tissue examination. These cases are found in various articles, and, in order to avoid duplication, are listed under the names of the authors as follows: Berg[3], who includes and cites Lundgren, Krepuska, Seiffert and Jeschek, 8 cases; Lattes and Waltner[15], who include and cite Kohlmeier and Czurda, Poppen and Riemenschneider, Capps, Rosenwasser, Kipkie, LeCompte, Lathrop and Sommers, Winship, Klopp and Jenkins, 18 cases; Brown[5], 6 cases; Amman[1], 1 case; Cleary[6], 1 case; Tamari *et al.*[21], 2 cases; Barton and Thee[2], 3 cases; Winship and Louzan[27] include and cite Proctor and Lindsey, Fuller, DeLisa, Bartels, Dockerty, Love and Patton, Lewis and Grant, 20 cases; Brown[4], 1 case; Weille and Lane[25], 3 cases; Mattick and Mattick[19], 2 cases; Mattick and Burke[18], 1 case; Graf[7], 5

*The opinions expressed in this publication are not necessarily those of the Department of the Navy or Department of Defense.

cases; and Tamari and Riggs (accepted for publication), 4 cases.

TABLE 1.—INCIDENCE OF NON-CHROMAFFIN PARAGANGLIOMA IN DIFFERENT AGE GROUPS AND SEX

Age	*Number*	*Male*	*Female*
10-19	4	0	4
20-29	9	4	5
30-39	13	7	6
40-49	16	5	11
50-59	16	1	15
60-69	8	1	7
70-79	4	1	3
80-89	2	1	1
Unknown (Seiffert)	1	0	1

This group of cases is too small in number to arrive at significant statistics but it would appear that the tumor, non-chromaffin paraganglioma, occurs most frequently in mid-adult life from 30 to 59 years of age and is approximately 2½ times more prevalent in the female. The increased incidence of the tumor in the 30 to 59 group seems to compare favorably with the incidence of the normal glomus jugulare in a similar age group as noted by Guild[10] in his most recent analyses of glomera, and further, tends to strengthen the impression of this tumor originating in the normal glomus jugulare.

There are 9 probable cases listed by Berg[3] and 3 cases by Graf[7]. Winship and Louzan[27] studied 42 cases of tumors of the glomus jugulare and derived data indicating that the onset varied from 19 to 80 years of age with an average age of 43.8 years, and that 80% of the tumors occurred in women. They also cite Bartels, who demonstrated a familial tendency in tumors of the glomus jugulare, or tumors of the carotid body, or both. Winship, Klopp and Jenkins[26] reported a case with metastasis to a cervical lymph node, while Lattes and Waltner[15] report a case with metastases to the liver. Kipkie[12] reported a patient with both an angiomatous tumor of the left ear and a carotid body tumor on the right, but did not feel it to be a metastatic manifestation. LeCompte[16], in studies upon tissue from 17 tumors of the carotid body and literature, finds no convincing evidence of a true chromaffin reaction; that apparently nerve endings are absent in the tumor tissue; that in 2 specimens which were analyzed for the presence of epinephrine, one showed a negligible amount, while the second had an epinephrine effect, probably due to some pressor substance other than epinephrine. He further states that the word "chromaffin" is a misnomer; that the carotid body is a chemoreceptor and not a gland of internal secretion, nor is it a part of the chromaffin system.

Histogenesis and Anatomy. In 1840, Valentin[22] described a localized swelling that resembled a ganglion at the initial portion of the tympanic nerve which he assumed was a collection of ganglion cells and suggested that this be termed the "ganglion tympanicum". Krause[14], in 1878, described somewhat similar swelling around the ramus tympanicus, consisting of a vascularized connective tissue and containing pyramid-shaped perithelial cells suggestive of a utricular formation similar to that structure known as the glandula inter-carotica. He suggested the name, glandula tympanica, for this structure. Watzka[24] recognized a similar structure in the tympanic canal adjacent to the tympanic nerve but classified this structure as belonging to connective tissue, in effect denying the existence of a glandula tympanica or paraganglion tympanicum.

The term paraganglion was first proposed by Kohn[13] pursuant to his study of extra-adrenal chromaffin tissue. In

his investigations of the morphology and embryology of the carotid body, he concluded that it arose in common with the anlage of the sympathetic ganglia, so that the term paraganglion was used to apply to a differentiated group of cells which at one time were indistinguishable from those which form ganglion cells. There is also mention of a paraganglion tympanicum.

The first complete accurate description of glomus formations in the temporal bone was accomplished, in 1941, by Guild[8] who wrote "Human temporal bone sections reveal structures, in several respects like the carotid body, for which the glomus jugularis is proposed. Usually they are in the adventitia of the dome of the jugular bulb, immediately below the body floor of the middle ear and near the ramus tympanicus of the glossopharangeal nerve. Usually there is but a single flattened ovoid glomus, about 0.5 mm. in the longer diameters and about 0.25 mm. thick. Occasionally two or more smaller bodies are present, sometimes one or all are in the canal that transmits the ramus tympanicus through the floor of the middle ear (in one case also along the course of this nerve over the cochlear promontory). Each glomus, wherever located, consists of blood vessels of capillary caliber with numerous epitheloid cells between the vessels. Usually, but not always, the vessels are the more prominent feature. Innervation and blood come from the same trunks that supply the carotid body; namely, glossopharyngeal nerve and ascending pharyngeal artery (through its inferior tympanic branch)." Lattes and Waltner[15] found two similar "glomus" formations in the adventitia of the jugular bulb in a 7-year-old male, which when properly treated gave a negative chromaffin reaction. Microscopic study of the middle ear tumor from a 47-year-old colored female gave negative reaction to chromates and a similar tumor in a 30-year-old white female contained a few scattered neurites in the neoplastic tissue. They further consider that the structures of the glomus jugulare, glomus tympanicum, glomus caroticum, paraganglium intravagale, juxtavagale of Muratori and paraganglium ciliare of Gosses are "Probably homologous parts of a system of organs consisting of masses of nonchromaffin tissue, closely associated with the parasympathetic division of the autonomic nervous system and its ganglia (3, 9, 10 cranial nerves)."

Zettergren and Lindström[28] have noted the glomus bodies situated near the tympanic artery and nerve, histologically resembling the carotid body; and that the glomus tympanicum is a rudimentary organ without any particular function, but that its chief significance is that it may be the site of origin of the middle ear tumor. In reviewing the available histories and surgical reports of the various authors, it is noted that the exact source of origin of the tumor cannot always be definitely ascertained. Some of the "nonchromaffin paraganglioma tumors" apparently arose from the dome of the jugular bulb, some from within the tympanic cavity without involvement of the jugular bulb, while others are of undetermined origin.

Pursuant to further investigation, Guild[9] wrote "The main points of clinical and surgical interest concerning the glomus jugulare that have been revealed by the additional study of normal material since the first report in 1941 are: (1) These structures occur not only along the nerve of Jacobson (tympanic branch of the glossopharyngeal) but also are about as frequently along the course of the nerve of Arnold (auricular branch of the vagus). (2) Slightly more than half

of them are in the adventitia of the dome of the jugulare bulb. (3) Along the nerve of Jacobson a glomus formation may be present, distal to its promontorial part, in the region where the nerve becomes continuous with the lesser superficial petrosal nerve near the geniculate ganglion of the seventh cranial nerve. (4) Along the nerve of Arnold a glomus formation may be present, at least as far distally as the crossing of the mastoid canaliculus and the descending part of the facial canal. (5) The observed normal variations in the location of glomus formations are sufficient to account for all of the differences that have been reported in patients with glomus jugulare tumors and for the differences in apparent origin that have been found at operation."

Hollinshead[11] after an extensive review of the literature notes that the abdominal chromaffin tissue is generally accepted as a true chromaffin tissue, exhibiting the ability to secrete a vasopressor substance (epinephrine) and that the weight of evidence is in favor of a neurogenic origin and that it is innervated by motor fibers (postganglionic) of the sympathetic system; whereas the carotid and cardio-aortic bodies are non-chromaffin, are presumably sensory in function and probably represent receptors that are sensitive to chemical changes in the blood.

Opinion is sharply divided as to the embryologic origin of the carotid body with respect to neurogenic tissue, as there is considerable difficulty in tracing wandering embryonic cells in the region of the branchial arches. Watzka[23] classified the carotid and aortic bodies as non-chromaffin and non-epinephrine producing paraganglia, suggesting that the term non-chromaffin paraganglia be adopted for the normal structures. Lattes and Waltner feel that the glomus caroticum, glomus jugulare, glomus aorticum, paraganglion intravagale and juxtavagale of Muratori, and paraganglion ciliare of Gosses are probably homologous tissues associated with the parasympathetic system and its ganglia; and that known tumors which arise from these organs are identical in histologic appearance and clinical behavior, and suggest that the term "non-chromaffin paraganglioma" be applied to the tumor.

Guild[10] has just published a very excellent and extensive report of further anatomical observations in 88 ears (44 persons) on the normal glomus jugulare. He notes that there is a marked tendency to bilateral similarity in the number of glomera encountered, that in 10 ears no glomera were found, but points out that these tissue specimens were deficient, and that race, sex or side of the head reveal no significant differences. It would appear that age may be a factor, in that the average number of glomera is largest in the period of mid-adult life. The histologic structure of the glomus jugulare presents a similar structure to that of the glomus caroticum. The innervation of the glomus jugulare is almost entirely supplied by non-medullated nerve fibers and many of the nerve fibers can be noted between the epitheloid cells, but the nerve endings cannot be demonstrated within the glomus. He feels that those glomera along the nerve of Jacobson are supplied by that nerve, whereas those along the nerve of Arnold might still receive their supply from the glossopharyngeal via its anastomotic connection or connections with the nerve of Arnold. However, this latter concept is to be considered at a later date. An interesting anatomical observation to otologists is that the nerve of Arnold dif-

fered in its course in more than two-fifths of these ears from that described in textbooks. It might course through one mastoid canaliculus, two mastoid canaliculi or present a branch or even all of the nerve might take a course "external" to the surface of the skull extending from the jugular fossa to the stylo-mastoid foramen, thus reaching the descending facial canal.

Pathology. The gross pathological appearance of these tumors involving the middle ear has no characteristic or outstanding feature. Upon observation of the tumor mass as it appears in the external canal, it is noted to be polypoid, varying from a grayish to a reddish color, of soft friable texture and with a strong tendency to bleed.

Histologically, these fundamental features are characteristic: an aveolar structure of the chief or epitheloid cells, and the epitheloid cells are usually large polygonal or rounded in shape with an abundant amount of cosinophilic cytoplasm and a rich vascular network. The nucleus of the epitheloid cell is usually comparatively small and generally vesicular. The epitheloid cell may also appear much smaller with a pyknotic nucleus. Mitotic figures are not usually found. The vascular channels are usually lined with a single row of endothelial cells which may be deficient in areas. Silver staining reveals a fine lacy argentaffin fibrillar network surrounding the nests of cells and vascular channels. Microscopically, most of these tumors show a tendency to mimic the structure of the normal carotid body.

For descriptive purposes, LeCompte[16] subdivided the tumors into 3 groups: (1) usual, with faithful reproduction of the normal carotid body; (2) adenoma-like, with "sheets" or "rows" of large polygonal cells and (3) angioma-like with smaller spindle-shaped chief cells adjacent to the vascular channels.

The tumor usually grows very slowly and has a tendency to recur if it is not completely removed. It is locally invasive, with occasional reports of extension into the brain. Metastatic lesions have been noted in the cervical lymph nodes by Winship, Klopp and Jenkins and to the liver by Lattes and Waltner. Kipkie noted separate tumors involving one ear and the carotid body but did not consider this a metastatic manifestation. Lundgren[17] states in his summary: "The pathologic picture is characterized by the extremely slow growth of the tumor. The tumor grows from the bulb of the jugular vein into the middle ear and causes a gradual impairment of hearing and increasing tinnitus. Earache and vestibular symptoms are rare. The tumor may go from the middle ear through the tympanic membrane and will then appear in the external auditory canal as an ordinary polyp, which, like the tumor itself, will bleed excessively if traumatized. It may, however, also grow in the opposite direction and destroy parts of the cell system in the mastoid process, sometimes with consequential facial palsy, and it may spare the labyrinth but nevertheless grow into the petrous bone".

Clinical Aspects. During the course of the disease patients may present the symptoms of aural discharge, itching, headache, dizziness, impaired hearing, tinnitus, hemorrhage and facial paralysis, all of which are nonspecific in that they are observed in infectious diseases or any condition in which the middle and external ear is occupied by a growing tissue mass. The chief clinical features are:

1. The extreme tendency to bleed following the slightest trauma, owing to the great vascularity of tumors.

Three of the cases on record had to be operated upon in two stages because of profuse bleeding during the operation. In the case of LeCompte, about 1000 cc. of blood was lost during the surgical procedure.

2. A subjective sense of pounding noise and pulsation in the ear (synchronous with the arterial pulse in our cases 6 and 7). These phenomena also must be ascribed to the great vascularity of the tumor.

3. The progressively expansive type of growth, leading in advanced stages to destruction of the temporal bone owing to pressure atrophy, and eventual extension into the cranial cavity with compression of the central nervous structures and of one or more cranial nerves. (See cases of Kipkie, Poppen and Riemenschneider, the first case of Kohlmeier, our cases 3, 8 and likely our case 4).

4. The possibility of metastases (case of Winship and our case 3).

5. The generally long duration of the symptoms, frequently associated with recurrences of the polypoid masses in the external canal following repeated removals. (In our case there was a 20-year history with 9 known recurrences).

Graf[7] divides the progress of the lesion into 4 stages: (1) tinnitus (often synchronous with the pulse), impaired hearing, and bulging and redness of the tympanic membrane; (2) tumor mass in the external canal which bleeds easily; (3) cranial nerve palsies, especially of the 7th, 9th, 10th, 11th and 12th nerves, seldom of the 5th and 6th nerves, occasionally with destruction of the labyrinth; (4) pressure on the brain. The history of symptoms usually amounts to several years before a diagnosis is made, and even then the patient may continue to live for many years. Nonetheless, the prognosis is not good.

One of our cases (Case 1) had an onset 15 years ago with tinnitus. He consistently refused all treatment but did acquiesce to a biopsy in order to substantiate the diagnosis. Our Case 2 has had symptoms, heralded by tinnitus, for 22 years. As early as 1934 the tympanic membrane was bulging and of a dull deep red color. Our Case 3 had an onset 5 years ago with facial paralysis, followed 2 years later by otorrhea and diminished hearing. On the other hand, our Case 4 presents a history of tinnitus and diminished hearing of only 4 months. All of our cases had tissue studies to confirm the diagnosis. The presenting symptoms at onset might be explained on the site of the origin of the tumor, however, any actively growing and expanding tumor must produce other symptoms.

The physical findings of a polyp in the external canal, facial paralysis, hearing impairment and otorrhea require no further comment. All polyps that are removed should be submitted for tissue examination, being sure the amount is adequate, yet keeping in mind certain dangers in "pulling" on other types of polyps, to confirm the diagnoses.

Berg[3] in his differential diagnoses of angiomatous tumors called attention to spontaneous pulsations in angioma, whereas it is not necessarily present in tympanic body tumors. Brown[5] also notes that "spontaneous" pulsation is sometimes present, but that a "pulsation sign" was elicited in all of his cases except one, by use of slight compression with a Bruening otoscope.

Roentgen-ray examination of these cases is not characteristic. During the earlier phases of the disease, it may only present a "slightly cloudy" shadow. Later, areas of rarefaction occur which give the impression of a "demineralization" of the pars mastoidea

and pars petrosa cells of being "rubbed into coalescence" or a dissolution and not spotty necrosis.

Treatment has been surgically exenteration of the tumor, which must be thorough, with a prolonged "follow-up" period of observation. A number of cases have been subjected to Roentgen-ray or radium therapy following surgical removal.

It has been noted by Winship; Klopp; Jenkins; Lundgren; Lewis and Grant; Weille and Lane; and Mattick and Mattick, that Roentgen-ray is ineffective. Graf feels that these tumors respond well to radiation in contrast to those of the carotid body.

Comment. It is our opinion that this tumor of the middle ear should be called "non-chromaffin paraganglioma" and that it originates in the normal glomus jugulare.

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"TATTOO"

A SURVEY OF SOME OF THE LITERATURE CONCERNING THE MEDICAL COMPLICATIONS OF TATTOOING

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TATTOO; the very word has a mystical lilt to it, and certainly its story throughout the ages of man has been fascinating. A badge which social anthropologists have traced back through all our civilizations, as far as 4000 B.C. (Hambly)[31] it has been found in such widely separated peoples as the Greenland Eskimo and the Polynesians. There is no doubt that tattoo plays a peculiar and fundamental part of the makeup of man.†

The true medical literature on tattoo dates back only one century to the pioneer work of Follin in 1849[26] and Hutin in 1853[34]. In the years that have followed there have been a great number of articles from French, German, British, American and Japanese authors.

This review will be confined chiefly to the medical complications of tattooing. The extensive work on the social, anthropological, and ethnological as-

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†Current interest in tattoos is exemplified by the review in Time, August 31, 1953, of Hans Ebensten's "Pierced Hearts and True Love" (British Book Centre $3) a short history of the tattooing profession.

pects of this subject will not be considered.

INCIDENCE. There is great need for a satisfactory statistical study of tattooing, and it is surprising that none exists. That the process is widespread, particularly in young men, and under conditions of military service, is readily apparent. An idea only, of the incidence can be given. In Honolulu, in 1943, between 300 and 500 men were being tattooed per day. This estimation by Within[91] was made up of 65% enlisted men of the United States Navy, 25% enlisted men United States Army and 10% defense workers to make the total. A further indication was given by Rukstinat[64], in 1941, when he analyzed a series of over 9,000 necropsy reports, performed in the Cook County Hospital for the period ending in 1924. He found that, in the white race, 8.79% of the males and 0.71% of the females were tattooed.

TABLE 1.—SOME COMPLICATIONS RESULTING FROM TATTOO

	Diagnosis	*No. of Cases*
1)	Primary syphilis	72
2)	Secondary syphilis	18
3)	Tertiary syphilis	1
4)	Tuberculosis	3
5)	Vaccinia	1
6)	Pyogenic infections	23
7)	Sarcoid	3
8)	Reticulo-histio-sarcoma	1
9)	Chronic discoid lupus erythematosus	4
10)	Psoriasis	1
11)	Melanoma	1
12)	Keloid	-
13)	Leprosy	3
14)	Mercurial sensitivity	18

INCIDENCE OF COMPLICATIONS. This must indeed be very low in relationship to the total numbers of persons tattooed. Some idea will be given by the following list (Table 1), an admittedly incomplete one, of the cases uncovered during the preparation of this review.

In connection with the statement that this list is incomplete, it is assumed that minor cases of mercurial sensitivity have been fairly common, but not reported. The incidence of keloid in the African Negro has probably been high.[24,38,41].

PIGMENTS OR DYES USED IN TATTOOING. A good list of the pigments or dyes used to produce the different colors in tattoos was included in Rostenberg, Brown and Caro's article[63] of 1950, and since it is the most complete, it will be reproduced here in full.

"*Blacks.* Carbon, finely dispersed, in an ammoniacal suspension. Phenol is also usually present.

Iron Oxide (C. I. 1311)*, also known as black oxide and magnetic oxide. It is ferroso-ferric oxide (Fe_3O_4 or $FeO \cdot Fe_2O_3$ or $Fe(OH)_2 \cdot Fe_2O_3$).

Logwood. Probably logwood black (C. I. 1253), also known as Campeche black, diamond black and neutral black and by many other names. This is an extract of logwood from the tree Haematoxylon campechianum. It is made into a lake with potassium dichromate, so that as it is applied there is a considerable amount of chromate present.

Blue. Cobaltous Aluminate (C. I. 1285). Co.O Al_2O_3, also known as azure blue and cobalt ultramarine and by many other names.

Brown. Ochre (C. I. 1267). A natural ferric hydrate and basic ferric sulfate containing alumina, silica and lime, among other substances. It occurs in a wide variety of shades and is sold

*The expression, C.I. 1311, stands for "Color Index" no. 1311, and similarly for the other C.I. numbers. The "Color Index" is the outstanding source of information in English on dyes and pigments. It is edited by F. M. Rowe and published by the Society of Dyers and Colourists, Yorkshire, England.

under many names, including ochre, with all sorts of descriptive adjectives, such as flame ochre and imperial ochre. It is also known as Chinese yellow, imperial yellow, sienna, mahogany brown, Roman earth, Mars yellow, Mars orange, Mars red, Mars brown.

Flesh. Iron Oxides. These, as a rule, are impure and are a variety of ochre (see under Brown).

Greens. Chrome Oxide Green (C. I. 1291). Chromic oxide or chromium sesquioxide (Cr_2O_3), also known as casalis green.

Guignet's Green (C. I. 1292). Hydrated chromium sesquioxide ($Cr_2O(OH)_4$ or mixtures of $Cr_4O_3(OH)_6$ and $Cr_4O(OH)_{10}$ with Cr_2O_3 together with 0.5 to 10% of boric acid. It is also known as emerald green and pannetiers green.

Phthalocyanine Dyes usually as copper salts and sometimes mixed with other coal tar dyes, especially Hansa yellow G (fanchon yellow; ext. D & C yellow #5*), which is alpha-(O-Nitro-p-tolylazo)-acetoacetanilide.

Reds. Cadmium Selenide. Also known as cadmium red (see C. I. 1272).

Cinnabar (C. I. 1280). Mercuric sulfide (HgS).

Sienna (C. I. 1267). See ochre under Brown.

Violet. Manganese Violet. (Probably) $NH_4Mn_2(P_2O_7)_2$.

Whites. Titanium White (C. I. 1264). Titanium dioxide (TiO_2).

Zinc White (C. I. 1262). Zinc Oxide (ZnO), also known as Chinese White.

Yellows. Cadmium Yellow (C. I. 1272). Cadmium sulfide (CdS), also known as radiant yellow. It may be also mixed with zinc sulfide and barium sulfate.

Ochre (C. I. 1267). See under Brown."

Certain additions and alterations to this list may be suggested. Cinnabar, or red mercuric sulfide, is synonymously known as Vermilion and as Chinese Red. Almost always used to produce the red color of tattoos, it is a brilliant red powder, which is insoluble in water and dilute acids, and is prepared by a process of sublimation of sulfur and mercury. Post[59] stated that cinnabar contained a little silicon, a trace of carbon, manganese and molybdenum, but no beryllium.

Another chemical, not mentioned in the list, used to produce the red color is carmine (carminum). This is an animal coloring matter derived from cochineal. It is also insoluble in water and has been used for staining techniques in microscopy.

The color that a pigment or dye transmits to the observing eye after the tattoo has been performed will be considered when the basic research of Guillaume[29] is discussed later in this paper. To identify a color in the skin correctly it is important to use incident, rather than transmitted, light.

Histochemical determination and other methods of identifying mercury in the tissues will be discussed in the section on mercurial sensitivity.

PATHOLOGICAL PHYSIOLOGY OF TATTOO. The most noteworthy contributions in this neglected field have come from the French author, Guillaume[29] in 1927. He has discussed the optical properties of the epidermis in detail, particularly with regard to fluorescence. The function of the stratum corneum was elaborated, and its thickness and the state of hydration were stated as varying directly with cutaneous fluorescence. The reason why a tattoo made with a black pigment appeared blue black to the examining eye was explained on the basis that the normal fluor-

*Ext. D & C yellow #5 refers to the official designation as it appears in the Coal Tar Color Regulations issued by the Food and Drug Administration, Federal Security Agency.

escence was reversed with the abundance of pigment in the dermis. The advice was given that it was best to examine black or deep brown colors, situated deeply in the dermis, with the aid of light of long wave length. To examine a superficial black or brown color, a light of short wave length, such as Wood's light, was preferable.

He also described the course and fate of pigment after being injected into the skin. Soluble pigment injected into the epidermis found its way right down to the basal layer, and from there migrated into the capillaries of the papillary body for excretion. Insoluble pigment injected into the epidermis did not follow this course but spread out at the site of injection and gradually moved up to the stratum corneum, and was then extruded in a manner similar to an epidermal cell, in its evolution from the basal layer to the stratum corneum. Consequently all epidermal tattoos must be temporary. Soluble pigment injected into the dermis again found its way to the blood vessels and was excreted. Insoluble pigment injected into the dermis gradually migrated to take up a perivascular position, and there formed masses of pigment with other collections. Thus the intervening areas, between blood vessels, tended to be free of pigment. The distribution of such masses was shown to be in the horizontal plane. Guillaume made use of the capillariscope to observe experimentally injected dye in the periungual region.

Further basic work was done by Brose[13] in 1927. He was concerned with the reaction of mechanical, chemical and actinic stimuli applied to tattoos. When a tattoo was subjected to a number of blows, the skin overlying the blue portions was observed to become raised whereas the red parts were unaffected. Covering the tattoo with a blue, or with a red cloth, and then rubbing the area, produced respectively swelling of the blue or red zones, with a lesser reaction in the other colored area. Similar results were obtained with the use of blue or red arc lamps. With the lamps, reflex reactions could also be elicited, insofar as irradiation stimuli to the normal arm would affect tattoos on the same forearm, in a manner similar to applying the stimulus directly there. Hot water acted as a stimulus in an identical way. Brose then suggested that these effects were mediated by the lymphatic or vascular systems. That such a vascular reactive role was a possibility was later borne out by Swinny[79] in 1946. Dealing with a case of generalized chronic dermatitis due to a mercurial reaction in the red part of a tattoo, he found that simply by stroking or gently massaging those areas produced immediate pruritic whealing flares, which lasted for 20 or 30 minutes.

The expression "*locus minoris resistentiae*" or area of lowered resistance, as first used by Lipschütz in 1906[42], has become generally accepted as a convenient way of describing that altered state in the dermis brought about by the injection of tattoo pigments. The physico-chemical, or other reassons, which determine the attractiveness of such areas for certain disease processes, have not been determined.

TECHNIQUE OF TATTOOING. The modern electric tattoo machine has been in use since 1890. This pistol-shaped instrument consists in essence of an electromagnetic device, similar to that used for an electric doorbell, in the butt, with a needle bar forming the barrel of the pistol. The needle bar ends in a group of fine steel needles, which are caused to vibrate upwards and downwards, penetrating the skin only to a depth of 1/64 or 1/32 of an inch, and operating at a vibration speed

of from 1000 to 3000 per minute. Thus the sensation is similar to that caused by a mosquito bite. Two machines, the outline puncher with from 2 to 4 needles, and the filler, with from 6 to 12 needles, are used for each tattoo. The latter does the shading work. A stencil is usually used for the design. Most machines do not have an automatic pigment filler, but such a modification was added by Conway[17] in 1948 for his medical tattoo machine. Pre- and postoperative care have always been minimal, and in some cases, much worse than that, and yet the incidence of pyogenic infections is very low, not one case having been reported in the last 50 years.

THE HISTOLOGICAL PICTURE OF TATTOO. Following immediately the process of tattooing, there has occurred a constant, acute inflammatory reaction, perhaps more due to actual physical injury than anything else. This has a duration of from one to two weeks, during which time the design is obscured by a sero-sanguinous exudate and crusts. The latter then become separated, leaving a relatively clear and clean tattoo. Usually the blue parts are level with the surface of the skin or else only slightly raised. However the red zone may remain slightly elevated for a longer period and may have some irritation persisting. This was illustrated to the extreme in Madden's case[46] when the reaction lasted 7 years. Microscopical studies of normal tattoos of a few weeks' duration have revealed that the pigment granules are collected in masses, largely in a perivascular location. The level of these masses in the corium varies, but most are in the upper layers, about midway between the epidermis and the roots of the hair follicles, or at about the level of the sebaceous glands. The pigment probably is contained largely in the macrophages. As mentioned, the areas between masses of pigment may be quite clear. Also the amount of pigment in a tattoo seen histologically strikes one as being much smaller than expected. No foreign body reaction to the pigment has ever been described, and it seems that the pigment exerts an extremely benign influence on the homeostasis of the dermis.

CLASSIFICATIONS OF COMPLICATIONS. Five different classifications have been suggested and are here presented.

1. Rook and Thomas[61], in 1952, proposed two groups. The first included diseases of transmission, such as pyogenic infections, syphilis, tuberculosis, leprosy, vaccinia and others. The second group included those diseases which tended to localize in a tattoo, and included secondary syphilis, psoriasis, lichen planus, allergic reactions to the pigments, lupus erythematosus, and a group described as foreign body reactions such as sarcoid and reticulosarcoma.

2. Lubeck and Epstein[44], in 1952, divided the cases into 3 general groups. The first included those due to mercurial sensitization; the second, those local or systemic diseases of transmission; the third, diseases associated with areas of lowered resistance (second group of Rook and Thomas).

3. Rostenberg, Brown and Caro[63], in 1950, proposed two groups. The first included accidents relevant to the tattooing process, the diseases of transmission. The second group was composed of 3 divisions, a) those diseases associated with an area of lowered resistance, b) foreign body reactions, c) mercurial sensitizations.

4. Madden[46], in 1949, suggested four groups. The first included the immediate reactions, the second the mercurial sensitizations, the third the diseases of transmission, and the fourth those

associated with an area of lowered resistance.

5. Sulzberger, Kanof and Baer[77], in 1944, did not attempt to give a complete classification but mentioned 2 groups of diseases that were noted in the older literature, first the diseases of transmission, as listed in the above classifications, and secondly, the pyogenic infections. They then went on to discuss the group in which their particular interest lay, the reactions due to hypersensitivity to the colored ingredients used in tattooing.

6. We propose a classification based upon time relationships, namely immediate, early and delayed reactions. *Group 1 (Immediate)* has been inserted for reasons of completeness, to show the acute constant inflammatory response, probably associated with physical tissue injury. This will not be considered further. *Group 2 (Early)* includes the transmission of local or systemic disease into the tattoo, with their time of appearance varying with the period of incubation. *Group 3 (Delayed)* is divided into 3 divisions: a) Diseases associated with areas of lowered resistance, b) Mercurial sensitivity reactions, c) Miscellaneous, containing sarcoid, reticulo-histio-sarcoma, papilloma, melanoma and keloid. The use of the term, foreign body reaction, in connection with a tattoo, was avoided. In this review all forms of syphilis will be discussed together for reasons of convenience.

GROUP 2: EARLY REACTIONS. *Syphilis.* The relationship between syphilis and tattoos has been a fascinating chapter in medical history, one in which certain fundamental facts about the behavior of syphilis have been revealed. In the first place, primary syphilis may appear in a tattoo in the form of a typical chancre, often multiple, due to the direct transmission of the organisms from an open lesion in an infected tattoo artist via the tattooing needle. Secondly, the lesions of secondary syphilis may arise in a tattoo, presumably due to preferential localization there because of the existence of an area of lowered resistance. Finally, syphilids thus localizing in a tattoo tend to avoid the red areas that have been produced by the use of red mercuric sulfide. In the latter case, there often may exist an interesting balance between the factors of attraction and those of repulsion, the summation of which may determine localization.

One of the classics in the history of the medical aspects of tattoos is the small book published by the French author, Hutin[34], in 1853 entitled "Recherches sur les tatouages." In it he described a case in which an infected tattoo artist, suffering probably from mucous patches of the mouth, used his own saliva to moisten the needles, and thus inoculated his patient successfully, not only with the desired pigment, but also with *Treponema pallidum.* This book also gave an account of the first instance of the medico-legal use of a tattoo. Other sections covered comments about the type of design, the technique, the coloring materials, the pathology and methods of removal of tattoos. At its end there was a statistical study of the location, color, permanence and duration of tattoos.

Josias[35], in 1877, described the first example of mass inoculation of syphilis, in which 9 men developed multiple chancres as a result of tattooing.

Philadelphia entered the picture at this time, with the classic report of 2 physicians, Maury and Dulles[48] in 1878. This meticulously prepared study concerned the mass transmission of syphilis in this manner, and remains a tribute to the high standard of medicine as practiced in Philadelphia at that time. It appeared in this journal,

(The American Journal of the Medical Sciences) even then in its 75th volume, coincidentally just 75 years ago. An itinerant tattoo artist practiced his trade in the area between New York, New Jersey, Philadelphia and Reading, and apparently being a real craftsman, his work was much in demand. However the appearance of several cases of primary syphilis appearing in his designs resulted in the careful public health investigation which followed. When located and examined he was found to be suffering from secondary syphilis with mucous patches in the mouth. It was his habit to use his own saliva, either to moisten the pigments, or else to apply to the design after tattooing. This latter practice was common in those days, since saliva was believed to have certain properties for promoting healing. Fifteen of his victims were tracked down who had developed primary chancres in their tattoos, from one to several lesions each. Most of these men also had erupted with secondary lesions. Four men were also located who did not develop the disease, even though the same technique had been used. Three other men had already been afflicted with the disease. The pigment used was vermilion, which is the same as cinnabar. No observations were made about the preferential localization of either the primary or the secondary lesions in the colored parts of the tattoos, the significance of which will be referred to later.

"Les Tatouages", another classic in this field, was published by Lacassagne[37] in 1881. A copy of this book has not yet been read, and reference can only be made to it through the work of other writers.

Three reports of similar occurrences in the military forces appeared next in the press. In 1886, writing of his experiences in the field, Arthur[4] collected a series of 41 extragenital chancres from the United States Army and the United States Navy, of which 26 had appeared in tattoos. Mucous patches were found in the mouth of the tattooer responsible. Barker[7], in 1889, from material in the British Army, listed 12 cases of primary chancres in tattoos. Some men had 2 chancres, one had 4, and in several, where a tattoo had been done on each arm, only one tattoo was affected. In 1889, as well, Whitehead[90] reporting from the Indian Army, described 5 similar cases. However 7 other men, who had been tattooed at the same time, escaped the infection.

Five chancres appearing in a tattoo was the subject of a case report by Cheinisse[14] in 1895, and Thomas[81] in 1898, reported 3 more cases of this kind.

Doubtless there have been many other cases of this sort, because syphilis was rife during the latter half of the 19th century. With the first half of the 20th century, however, a tremendous change has come about: the control of syphilis, and with it the incidence of syphilis in tattoos has dwindled to nothing.

The peculiar behavior of secondary syphilis in locating preferentially in tattoos was probably first noticed by Rona[60] of Budapest in 1898. Shortly afterwards, Zechmeister[93], in 1901, and Wechselmann[88], in 1905, described similar findings. Lipschütz[42], in 1906, reported a further case, and was the first to put forth the theory of "*locus minoris resistentiae*" as a means of explaining the phenomenon.

Dohi[20], a Japanese author, in 1909, carried these observations one step further. He noted that a papular secondary syphilid, in a man 35 years of age, who had been tattooed at the age of 19, was most prominent in the blue parts of his tattooing, and that the red

areas were not involved. This recognition of the protective influence of the red mercuric sulfide has since been observed on many occasions. In these further reports there will also occur what appear to be conflicting reports, where there are lesions in both the blue and the red colored zones. However 2 facts should be borne in mind. The first is that other chemicals than cinnabar, and not containing mercury, can be used to produce a red color, and secondly, as already mentioned, the summation effect of the attractive and of the repulsive effects may weigh in the balance toward the former. Belote[9] has however stated that where secondary syphilitic lesions have occurred in the red portions of a tattoo, the dye used to produce that red color has never been proven to be cinnabar.

Florange[25], in 1909, reported 2 cases, the first of which showed the sparing action of the red pigment, but the second showed lesions in both colors, although the blue involvement was more marked.

Three cases described by Holland[33], in 1911, showed that a papular syphilid was most prominent in the dark parts of a tattoo. However, a fourth case in his series showed lesions in both color zones.

Aoki[2], in 1912, confirmed the previous work of his fellow countryman, Dohi. Experimentally, working with rabbits, he was able to demonstrate that secondary syphilitic lesions were accentuated in the blue, and absent in the red parts of tattoos. The pigment in use was cinnabar. He also reported another human case with this sparing effect.

Bernheim and Glück[11], in 1912, presented one case with involvement of the blue part of a tattoo, and in 1918, Keidel and Zimmermann[36] described the marked involvement of the blue zones of a tattoo, with, however, a few papules in the red area. Spillmann, Drouet and Diot[74] then reported a case that showed lesions in the red portions only.

Noel[51] gave a discussion of the previous literature in 1927, and as well presented another case. He mentioned the possibility that the case reported by Spillmann *et al.* might have been due to sensitivity to cinnabar. He also mentioned that secondary syphilitic lesions have shown a tendency to localize in other areas subjected to trauma. In this connection may be mentioned the well known phenomenon, the corona veneris, and areas of macerated skin, where often the most florid secondary eruptions have occurred.

An important paper by Belote[9] followed, in 1928, in which he described 2 additional cases of sparing of the red zones. He discussed the balance between the lowered resistance state and the protective influence of the mercury. The first microphotograph on this subject was reproduced.

Another paper by Dohi[20], in 1926, and one by Vigne and Dusan[87] reported cases where the cinnabar areas were spared.

A valuable contribution to the literature was made by the report of Rukstinat[64] in 1941. This included a comprehensive review of tattoo in relation to syphilis, a good coverage of the ethnological aspects and a careful presentation of the complications. Other factors, such as motivations, permanence, fading and pigments in use were mentioned. The purpose of his paper was, however, to investigate statistically the relationship of tattoos and scars as indicators of syphilis. The figures in brief have already been given in the introduction to this review. He was able to refute the old belief that tattoos were an indication of the coexistence of syphilis, more so than

penile scars or scars of cutaneous syphilids.

A recent report by Lubeck and Epstein[44] described a case in which all the colors in a tattoo were involved. However, it was stated that the tattooing had been done in Hawaii, where apparently cinnabar is not used to produce the red color.

As would be expected there is a paucity of reports of tertiary syphilis localizing in a tattoo. One such case was reported by Diss[19] in 1926.

Tuberculosis. Only a few cases of tuberculosis involving a tattoo have been reported, and these occurred at the turn of the century.

An oft-quoted English series was reported by Collings and Murray[16] in 1895. A 15-year-old boy, suffering from far advanced pulmonary tuberculosis, tattooed his 2 younger brothers, aged 13 and 10 years, and a friend, aged 15 years. He held India ink pigment in his palm and used his own saliva to make a suspension of the dye. Five weeks later, the older of the 2 brothers developed a mass of white pustules in the rose area of his tattoo, with the remaining area being scarred and covered with white "scabs." The younger brother showed a tattoo whose whole pattern was raised and covered with "scabs," from under which in many areas pus escaped. The third boy presented a similar picture to the one just described. However, he applied a poultice to the area, and in a week's time, showed a group of deep ulcers, which had hard, rounded edges and a granulating base. All 3 boys had enlarged epicondylar and axillary lymph nodes. A pathological report of a biopsy from the third case mentioned well-marked giant cells, just under the malpighian layer, although the presence of tubercle bacilli was not demonstrated. These cases were shown at the renowned clinic of Jonathan Hutchinson, and the diagnosis was confirmed.

Dore[21], in 1918, reported fully a case of cutaneous tuberculosis following tattooing. It was the same case that had been briefly reported in 1913[21]. The patient had been tattooed in 1908, with a "touch-up" job being done 3 years later. The first sign was noticed in 1913, and consisted of a minor swelling in the tattoo on one forearm, followed by the appearance of minute raised spots in the same area, and then in the tattoo on the other forearm. The lesion in the first tattoo then developed further to form a raised plaque with well-defined edges and a flat ulcerated surface, being about one inch by one-half inch in size. The remainder of the tattoo on this forearm, and the whole tattoo on the other, also showed small conical papules, which had minute central depressions, giving them the appearance of papulo-necrotic tuberculids. All the lesions were confined to the tattooed areas, and were stated as corresponding in location to the areas that had been "touched-up". The patient also had a chain of enlarged lymph nodes in the right axilla. The ulcer was excised, and on histopathological examination, was stated to have the characteristics of tuberculosis. Dore mentioned here that Heller, as quoted by Ullmann[83], in 1903, had seen a case, of similar nature, which had been treated, presumably for its immediate inflammatory response, with cow's milk. He also stated that Jadassohn had described a further similar case, in which the tattoo artist had used saliva to moisten his pigments.

Mallam[47], in 1922, produced a case of a reaction in a tattoo, in which his own diagnosis was papilloma. However Dr. Gray and Dr. O'Donovan gave their opinion that the lesion was probably lupus verrucosus. This case

report has been included in the Group 3, c) division, on account of this divergence of opinion.

Pyogenic Infections. The scarcity of pyogenic infections complicating tattoos is remarkable when one considers the sketchy methods of antisepsis in use in most tattoo parlors in the older days. It is conceivable that the intense immediate inflammatory response and certain of the pigments used may sometimes exert a bactericidal action.

"Histoire Medicale due Tatouage", published by Berchon[10] in 1869, is a fine example of excellent pioneer writing. The author, a medical officer in the French Navy, had already produced over 30 articles on general medicine, anthropology and natural history, a formidable accomplishment in those days. This rare volume of 184 pages covered the following phases of tattooing: history, anatomy, physiology, medicolegal study, pathology and surgery. Berchon then described his own series of cases of inflammation following tattooing. There were 17 cases of inflammation, of which 9 would appear to have been the acute inflammatory, non-suppurative variety. In 8 others, suppuration was quite definitely mentioned. Besides these, he listed 8 cases of gangrene, and 4 others which required amputation. He then added 7 other cases, in which death ensued, 4 following amputation but all directly attributable to the tattooing process. An important note was that 3 of the deaths followed abruptly after the application of very large tattoo designs. The numbers of the cases, given above, correspond with those quoted by Rook and Thomas[61].

Only one case of erysipelas occurring as a complication has been reported, and that was by Sehrwald[68] in 1913.

Leprosy. "Though leprosy is one of the oldest known diseases, there is still uncertainty and confusion concerning its transmission and the incubation period." This statement was made by Porritt and Olsen[58] in their article in 1947 describing their 2 cases of leprosy, believed to have been transmitted by tattooing. Two young United States Marines had been tattooed successively by the same man in Melbourne, Australia, in 1943. Both developed cutaneous tuberculoid leprosy, 2½ years later. A third Marine, tattooed at the same establishment but not on the same day, has not shown any evidence of the disease. A complete description of the pathological picture in the biopsy material was given, which was reported by the United States Marine Hospital (Leprosarium) at Carville, Louisiana, with the unequivocal diagnosis of typical tuberculoid leprosy.

Whether transmission was affected by the tattooing or not cannot be said with certainty, but as the authors have brought out, "these 2 cases provide striking evidence for the spread of leprosy by inoculation." It had been known, of course, that leprosy tended to localize in scars, and that it could be activated by trauma. The long incubation was explained by the presence of considerable resistance on the part of the 2 patients. It was also suggested that the extensive traumatization of the skin might have favored the development of the disease, and that the multiple skin punctures might also have permitted a massive inoculation. It was obvious that the red mercuric sulfide served no protective function against leprosy.

Mitsuda[49], in 1928, reported a case of leprosy occurring in a tattoo.

Vaccinia. Wilde[92], in 1929, described a case in which a vaccinia reaction occurred in a tattoo which had been done 3 weeks previous to a vaccination for smallpox. The resulting reaction was severe and extensive, and when it

healed, it was found that the tattoo had been removed by the inflammatory process. Wilde also mentioned a case of chancroid occurring in a tattoo.

GROUP 3: DELAYED REACTIONS a) LOWERED RESISTANCE STATES. Certain views explaining in part the concept of "*locus minoris resistentiae*" have already been presented.

Chronic discoid lupus erythematosus. The first description of this complication was detailed by Hall[30] in 1943. His case occurred in a 35-year-old man, who had been tattooed 19 years before. Three years before the case was presented the man noticed some roughness of the surface of the red portions of his tattoo, which then became elevated. Later these areas showed some stippling, with dilated follicular openings, filled with keratotic plugs. The histological picture was described as consistent with, but not characteristic of, lupus erythematosus.

Madden[46], whose writing in this field has been authoritative, in 1949, described the case of a 36-year-old man, who had been tattooed 6 years previously. Following the initial inflammatory reaction, healing had followed. Four years later, however, the patient first noticed an itching and burning sensation of the red parts of his tattoo, accompanied by an eruption on his face with the same subjective symptoms. This reaction persisted for several months, at which time the patient showed "scattered, pea-sized to dime-sized, dry, round, erythematous, pruritic papules, covered with an adherent, carpet-tack-like scale" on the face and also in the tattoo. It was stated that biopsy specimens from the face and the tattoo showed histopathological features which were in keeping with the diagnosis of chronic discoid lupus erythematosus. Furthermore on 2 occasions, on exposure to the sun, there was an acute flare-up of the eruption in both areas, even though the tattoo had been protected by a shirt and a heavy leather jacket.

The third case was reported by Rook and Thomas[61] in 1951. A 24-year-old man had been tattooed 7 years previously with the application of a blue and red design on his forearm. Three months before the case was presented, he noticed the abrupt appearance of red patches on both cheeks which in the next few weeks enlarged rapidly. At precisely the same time as the onset of the cheek eruption he noticed a moderately severe persistent irritation in the tattoo. Then after a week he noticed that the red areas of the tattoo were becoming raised and warty, with increase in those signs in the next 3 weeks. The blue areas were not affected. A patch test to 2% ammoniated mercury ointment was strongly positive. A biopsy specimen was taken from one of the red areas in the tattoo, and was reported by Dr. I. W. Whimster as follows: There was severe, generalized, irregular epidermal hyperplasia, subepidermal edema, vascular dilatation and local infiltration by lymphocytes. There was much pigment in the upper layers of the dermis, which by transmitted light appeared black, but, by incident light, orange-red. It was considered that this pigment was identical in color with vermilion. A second biopsy specimen showed similar changes except that in the center of the lesion there was no pigment, and also no inflammation or hyperplasia. In the inflamed area there was mild fibrinoid degeneration of the subepidermal connective tissue. In both sections the findings were considered to be compatible with the diagnosis of lupus erythematosus. A biopsy specimen from a facial lesion showed a flattened epidermis with keratotic plugging of the follicles. There was a marked lymphocytic infiltration, mainly

about the cutaneous appendages. In their second paper[61] Rook and Thomas have added some comments about their case as follows, "It is doubtful whether the appearance of lupus erythematosus in the tattoo in this patient should be regarded as an isomorphic phenomenon, or whether sensitivity to mercury is a causative factor in the lupus erythematosus. In favor of the latter alternative is the restriction of a reaction to the red areas of the tattoo, and the presence of a strongly positive patch test to ammoniated mercury in the second patient."

The most recent case was described by Lubeck and Epstein[44] in 1952. The patient was a 30-year-old man, who had been tattooed at the age of 18. Six months before the case presentation, typical lesions of chronic discoid lupus erythematosus developed in the butterfly distribution areas of the face. A non-medical advisor suggested the use of ultraviolet light therapy. This caused a violent exacerbation of the facial lesions, and then for the first time similar lesions appeared in the red areas of his tattoo. The morphology was mentioned as typical, with sharp margination, erythema, follicular plugging and also telangiectasia.

Several interesting observations have been made in these case reports, which might have some significance when considering the etiology of lupus erythematosus. The affinity of those lesions only for a red colored pigment, the photosensitivity, the relation to mercury sensitivity would seem to warrant further investigation.

Psoriasis. Case reports on psoriasis and lichen planus are very sparse in the literature. In 1940, Telichevsky[80] reported the case of a 20-year-old man, who developed acute generalized psoriasis for the first time in 1939. During the extended course of his eruption, numerous efflorescences appeared in the lines of tattoos on each forearm, thus showing the Köbner phenomenon.

b) MERCURIAL SENSITIVITY REACTION. Often a young man's first act of sexual prowess has been commemorated by means of a suitable tattoo. Unfortunately the old saying, "A night with Venus and the rest of your life with Mercury" has often held true for the tattoo itself, for by far the commonest complication of tattooing, apart from the immediate response, has been mercurial sensitivity reactions.

Pathological Picture. As mentioned earlier, often the red portions of a tattoo have remained elevated and irritable for considerable periods of time. Indeed, in Madden's case[46] this persisted for 7 years until the tattoo was excised. Usually, however, the swelling and irritation subside in a few days and then the tattoo enters a latent period. Occasionally the use of a mercurial preparation elsewhere on the skin, or taken internally, has induced a violent hypersensitivity reaction in the tattoo. More usually the onset has been spontaneous and no exciting factor has been incriminated. The red areas in such cases have developed abrupt severe irritation and considerable swelling, closely localized to the zones concerned. This has often progressed to warty growths, eczematization and occasionally to tumor formation. The histological picture has shown a severe, chronic nonspecific inflammatory reaction. The epidermis has shown hyperkeratosis and parakeratosis with considerable acanthosis. The middle and lower corium have shown a different cellular reaction from that seen in the uncomplicated tattoo, in that considerable numbers of eosinophils, plasma cells and fibroblasts are present, in addition to the lymphocytes. There has been seen an associated edema of the upper

corium with dilated blood vessels, particularly in the papillary bodies.

Determination of mercury in tissues. A suitable process has been described by Hand, Edwards and Caley[32] in 1943, in which they have stated that the simplest and most reliable procedure for the identification of mercuric mercury required its precipitation from unfixed frozen sections of tissue, by means of stannous chloride solution, and then microscopic identification. "As has been pointed out by Zwick and Emich, the microscopical appearance of finely divided mercury is highly characteristic. The particles are spherical, black and non-refractile. When sufficiently large an image of the lens of the objective is reflected from their centers. Their very roundness makes them subject to ready displacement, however, and the section is best cut rather thick (15 microns) if free mercury is suspected, in order that a comparatively undisturbed inner zone may be available for inspection. Zwick demonstrated that metallic mercury is present in the subcutaneous tissue after inunction of the element in a salve vehicle. We have confirmed this observation. He pointed out that the globules react with components of tissue fluids and lose their spherical shape. According to Christheller, they dissolve completely in tincture of iodine and this characteristic reaction may be observed under the microscope. We have observed further that solutions of chlorauric acid react with the minute spheres, causing at first a loss of gloss and a roughening of the surface; this is followed by a gradual disintegration of the spheres as gold amalgam forms. These changes were observed in sections of tissue. The above mentioned characteristic microscopic appearance and microchemical behaviour permit positive identification of the metal."

Rook and Thomas have mentioned the possibility of an organic mercurial compound derived intracellularly from cinnabar. Ellis and Robinson[22] have stated that "patients may apparently become sensitized to the complex mercurial compounds without reacting to the simple, inorganic or to the other complex organic mercurials." Sulzberger, Kanof and Baer[77] have reported that "Our case and the majority of cases thus far reported do not reveal reaction to patch tests with the mercurial actually used in the tattooing, red mercuric sulfide or cinnabar (2 exceptions); they do reveal reaction to other more soluble and more highly dissociated mercurials. Cinnabar can produce the sensitizations and can elicit allergic reactions, both clinically and, occasionally, on patch tests. This is proof of the specific biologic effect of this mercurial and also indicates that this material has a certain degree of solubility in the tissue fluids." So much for the conjecture about the form that mercury takes in the tissues.

Spectroscopic examination. This procedure requires the digestion of the tissue with acid. Dithiazone solution is then employed to mix with the digest and then the extract is measured with the spectrophotometer.

Differential tissue staining. Perle's reaction may be used to exclude ferruginous pigment, and the dopa reaction to exclude melanin.

Polarizing microscope. Doubly refractile granules, such as silica, can be eliminated.

Patch testing. This has been widely employed as an aid to the diagnosis of mercurial sensitivity reaction. It will be further referred to when the work of the individual contributors is discussed.

CASE REPORTS. The first probable case of a mercurial reaction in a tattoo was reported by Welander[89] in 1893, and

later the same author described another case in 1907. The case reports of Ullmann[83], in 1903, and Valder[85] were similar to Welander's.

In 1930, Unna[84] opened up a new field of thought and investigation, when he considered mercury as an allergen, and instituted the used of the patch test for confirmation. He reported the case of a man, 63 years of age, who had been tattooed in his youth. At the age of 40 he was treated for syphilis by means of mercurial inunctions without any ill effects. At the age of 60 he used wet packs of mercuric bichloride solution to treat his hemorrhoids. A severe acute dermatitis occurred in the perineal area, to be followed by a similar eruption, confined entirely to the red areas of his tattoo. A skin test with a mercury plaster was positive.

Shaffer[69], in 1928, was the first American author to describe a case of tattoo dermatitis due to mercury. However the investigation was not completed.

Ballin[6], in 1933, reported a case in which the red part of a 2-year-old tattoo presented a 2-months-old eczematous process, with no allergen being readily apparent. The lesion subsided and was later reproduced by the application, elsewhere on the skin, of 2% ammoniated mercury ointment, and of a 1:1000 solution of corrosive sublimate.

A case of tattoo dermatitis, confined to the red zones was presented by Sulzberger[76] in 1937. There were positive eczematous patch test responses to ammoniated mercury ointment, to a 1:1000 solution of mercuric bichloride in water and to cinnabar powder.

Two German reports followed, those of Müller[50] and Schmitz[66] in 1938, which, like Ullmann's case showed tumor-like lesions.

In the first of his 2 reports on reactions in tattoos, Madden[46], in 1939, described a tumor formation in the cinnabar part of a tattoo. This was the case with the persistent irritation and elevation right from the time of operation until 7 years later when excised. Patch tests were positive to 2% ammoniated mercury ointment, to mild mercurous chloride, to 1:1000 aqueous solution of mercury bichloride and to strong mercurial ointment, U.S.P. Patch test was negative to 2% mercuric sulfide.

In 1943, Rulison[65] and Coombs[18] reported 2 cases of mercurial sensitivity reactions in tattoos.

The first case of a generalized reaction attributed to the mercury used in the red part of a tattoo was described by Novy[52] in 1944. Associated was a toxic nephritis. A positive patch test to cinnabar was obtained.

Sulzberger, Kanof and Baer[77], in 1944, gave a comprehensive review of hypersensitivity to the colored ingredients of tattoos. A case of their own was added to the list and is the first example of decreasing sensitivity to the mercury allergen, although exposure remained continual. The first patch tests showed negative reactions to cinnabar and to 2% mercurochrome; they were one to two plus for calomel powder, for 1:1000 mercuric bichloride solution in water, and were positive or negative to 10% ammoniated mercury in yellow vaseline. The patient then showed clinical improvement, with little infiltration, scaling and crust, and only slight elevation of the red parts of the tattoo remaining. The patch tests were then re-applied and a questionable or negative response was obtained to the mercury bichloride alone.

A further variant was introduced by Swinny[79] in 1946, in which a generalized chronic dermatitis was associated with a tattoo whose red portions were shown to be highly irritable. Stroking or gently massaging the affected red areas caused immediate pruritic whealing flares, which last up to a half an

hour. Contact tests were positive to 2% ammoniated mercury ointment and to a 1:1000 solution of bichloride of mercury. On excision of the tattoo the entire dermatitis cleared up, without later recurrence.

A review article by MacKenna[45], in 1948, discussed the technical allergic basis for this sensitivity reaction. He also added another case. A comment was made to explain why tattoos made with India ink appear blue, and he suggested the black color of the ink being modified by the color of the blood in the venous plexuses of the skin as the reason.

A reaction to a green-colored pigment, the first in the literature, was reported by Rostenberg, Brown and Caro[63] in 1950. Unfortunately identification of the green pigment was not carried out.

A German author, Schönfeld[67], has made fine contributions, both to the medical and the social anthropological aspects of this field. In 1951 he described 2 further cases of tattoo reactions in the red areas. In one case patch tests were positive to mercury solutions but not to cinnabar ointment.

The most recent work of Lubeck and Epstein[44], in 1952, described another case of this kind. It concerned a 24-year-old man, who had been tattooed 7 years previously, and according to the patient, the red areas had remained swollen right from the time of tattooing, although they gradually became worse. A biopsy, done in 1950, was reported as acute, non-specific dermatitis. When first seen in 1951, he showed five, discrete, moderately raised, red, crusted areas in the red parts of his tattoo, and one similar lesion in a blue zone. Patch tests were performed with a 1:1000 solution of mercuric bichloride, and with 4% ammoniated mercury in zinc oxide, and a 4 + reaction was obtained to each in 24 hours. The lesions were excised surgically.

The section on mercurial sensitivity reactions will be concluded by a summary of a case report by Beerman, Lane and Mescon[8], which is expected to be published in the future. This concerns the development of a large granulomatous lesion which developed in the red parts of a tattoo over the course of about one year. The lesion measured approximately 4½ by 3½ inches. A spectroscopic analysis of the tissue was made and showed a positive reaction for mercury. It is believed that this is the first case report of a mercurial sensitivity reaction occurring in a tattoo in which this means of confirmation of the presence of mercury in the actual tattoo has been carried out. The pathological report may be described as follows. There was a considerable amount of parakeratosis, evident particularly in the numerous plugged hair follicles. The epidermis was alternately thickened and atrophic, the former zones in association with hair follicles, and the latter zones overlying areas of fairly dense cellular infiltration in the upper portion of the corium. Pigment collections are seen grouped together in the upper part of the corium in a well-marked zone, about the level of the sebaceous glands, and showing a tendency to run parallel to the surface of the epidermis. The pigment seemed to be contained in large macrophages. The color seen by transmitted light was a dark brownish-black, but under incident light, showed up beautifully like specks of highly burnished copper. The pigment cells were arranged in a well-marked perivascular formation. The cellular infiltrate is confined to the upper section of the corium, both in relation to the collections of pigment cells, and also extending upwards into the papillary bodies, often in a rather dense infiltra-

tion, and also being well marked about the pilosebaceous structures. The cells concerned are chiefly lymphocytes and histiocytes, with a goodly number of plasma cells, and of course, the pigment cells. Eosinophils were not prominent. In the upper portion of the corium the infiltration in the papillary bodies often is more homogeneous, whereas lower, it occurs more in the form of separated islands of cells, the areas intervening being practically free of pigment or of infiltrate. At the base of one follicle is a well-marked foreign body reaction with several Langhans giant cells, but this is probably not a fundamental part of the reaction. Excision of this mass has apparently been completely successful.

MISCELLANEOUS GROUP. *Sarcoid.* Sarcoid reaction in a tattoo was first reported by Madden[46] in 1939 when he described the case of a 27-year-old man, who had been tattooed 7 years previously. He developed dark red, elevated nodules, covered with dry, glistening skin, in the tattoo only. A biopsy specimen revealed the lesion to have moderate hyperkeratosis on a thin epidermis, which was otherwise normal. The corium and subcutaneous tissue showed round or oval clusters of epithelioid cells, like those seen in the sarcoid of Boeck. This was well shown in the low-power microphotograph. Small lymphocytes were scattered in and around the above clusters, and no necrosis was present.

A second case can be included only with reserve for the additional factor of the presence of silica has been added. Sweet[78], in 1950, presented a case report about a man, who had been blown up by a mine in 1945, at which time he suffered extensive accidental tattooing. Four years later he developed firm, painless swellings on the face, hands, forearms, enlarged lymph glands of the epitrochlear, axillary and neck areas, along with evidence of hilar gland enlargement. He also suffered loss of vision of one eye, and a roentgenogram of one finger showed bony involvement. A biopsy specimen was reported by Dr. I. W. Whimster as follows, "The dermis contains many discrete and confluent foci of tuberculoid granulation tissue, in which are several areas of necrosis, many appear to have arisen in the connective tissue between the tubercles rather than inside them. Scattered throughout the lesion, and to a lesser extent the adjacent skin, are many, variable sized, polyhedral, doubly refractile, crystalline particles, a few of which are within giant cells. No acid fast bacilli could be demonstrated." The histopathological remarks about the lymphatic gland were, "Most of the gland tissue is replaced by confluent and discrete foci of histiocytes, with giant cells, lymphocytes and eosinophils. There are no areas of necrosis, nor any doubly refractile particles." Unfortunately there was little reference to the tattoo component of this case, but even so it would seem probable that the sarcoid reaction was due to the silica.

A case of Boeck's sarcoid was reported by Lubeck and Epstein[44] in 1952. This was in a 52-year-old man, 20 years following tattooing in which the first signs were elevated, thickened and scaly lesions, confined to the red, green and blue parts of the tattoos. The latter were on both arms and on the chest and were not completely involved by the reaction. He also suffered from ocular, pulmonary, lymph gland and bone involvement. A biopsy specimen was taken from one of the lesions on the elevated portion of the tattoo. The histopathological findings revealed a chronic granulomatous infiltrate, in which were found numerous epitheliod cells and numerous giant cells, of the

Langhans type. There were no areas of necrosis. The section was reported as probably a sarcoid reaction. This case was treated with cortisone, which apparently caused marked alleviation of the symptoms and signs.

A most interesting case report, involving the possibility of galvanic exchange between a vitallium plate and the mercury of a tattoo, was described by Post[59] in 1952. This occurred in a 30-year-old man, who had been tattooed in 1941 with a red and blue design on each forearm. A fracture of the left radius in 1947 was treated successfully by means of the insertion of a vitallium plate. In 1951, firm nodules appeared, in the red areas only, of the tattoo on the left forearm, gradually increasing in number, and also showing some eczematization. The possibility of a galvanic exchange was considered and as a result, the plate was removed in December, 1951, 5 months after the onset of the eruption. This resulted in slow but definite improvement. It should be mentioned that only those red parts which were in close relationship anatomically with the plate were affected, the remainder of the red area of the tattoo on the left forearm, all the blue areas of both tattoos, and the tattoo on the right forearm were not involved. "Biopsy revealed that the epidermis was locally parakeratotic, edematous and slightly infiltrated with leukocytes. In the cutis, there were scattered cells, which contained a black pigment, evidently the result of the tattoo. There was also a granulomatous infiltrate in the cutis. A granuloma which surrounds a hair follicle and penetrated deep into the specimen was composed of numerous epithelial tubercles, composed of histiocytes, many of which contained pigment. A number of giant cells were present. A peripheral zone of lymphocytic infiltration was present. Pigment was also found in some of the giant cells. A smaller subepidermal epithelioid granuloma was noted containing less pigment. Morphologically the lesion resembled a sarcoid." Further investigation showed that the plate and screws were made of vitallium, which had remained free of any electrolytic or galvanic change. Vitallium was also stated as being non-electrolytic and non-galvanic. For purpose of exclusion, it was also pointed out that neither vitallium nor cinnabar contained any beryllium.

Reticulo-histio-sarcoma. A Canadian author, Auger[5], in 1943, reported the only case of reticulosarcoma occurring in a tattoo. The patient was a man, 33 years of age, who had been tattooed in a blue color on the forearm at the age of 16. In a few months, before the case was first seen, a tumor developed in the tattoo and enlarged to the size of 3 by 2 cm. The tumor was surgically removed and there was no evidence of recurrence 4 years later. The surgical specimen was described histopathologically, in part, as follows: "The lesion consisted of a sarcoma in the dermal-subcutis level. It was lobulated and relatively well demarcated by means of a sclerotic margin. The cell type was a cell, rounded or elongated with clear, scanty cytoplasm, and a round or elongated nucleus. Mitotic figures were numerous, and small areas of necrosis were present. Invasion of the adipose tissue had occurred. Certain of the tumor cells contained pigment, an evidence of the phagocytic function of the reticuloendothelial elements of the tumor." This section was reviewed by one of us (H.B.), who has concurred in that diagnosis. Auger mentioned the possibility of chronic irritation by the pigment granules causing the development of this lesion, and listed chimney sweep's and mule-spinner's cancers as

possible analogies. He also spoke of the keloid formation following tattooing in Negroes, which will be referred to in the next section.

Keloid. In the French literature, there have been several papers dealing with the development of keloids, of varying sizes, in the African Negro, following tattooing.

In 1937, Cipollaro[15] described a case of keloid developing in a young man following the removal of a tattoo by means of first using carbon dioxide snow, then curetting and applying a tannic acid, silver nitrate solution. Whether the keloid had anything to do with the tattoo or the treatment does not seem clear.

Malignant Melanoma. A case of accidental tattooing, in which a 9-year-old boy punctured the skin of his forehead with the tip of an indelible pencil, subsequently developing the present lesion, was presented by Sharlit[70] in 1938. In 3 months, the mark which resulted grew to the size of 0.6 cm. in diameter, and was brownish and elevated. A biopsy of the excised lesion resulted in a diagnosis of malignant melanoma. The report mentioned thick masses of pigment in the cutis, with the staining and chemical characteristics of melanin. The cells were partly, irregularly elongated elements, and partly large, round to oval cells, with rather clear round nuclei. Occasional dendritic forms were seen. The relationship of these cells to the basal layer of the epidermis was given. Additional opinions on the biopsy specimen were given as, benign melanoma, or pigmentation with melanin secondary to an old inflammatory lesion. However it seemed probable that the diagnosis was malignant melanoma.

Papilloma. Mallam[47], in 1922, described a 33-year-old man, who had been tattooed on both forearms 7 years before, and who, 2 years later, developed a number of warty growths in the tattoo of one forearm. These continued to grow and were carefully confined to the red areas only of his tattoo. The lesions developed cracks and small necrotic areas but showed no exudate, discharge or involvement of the lymph nodes. The pigment was proven to be cinnabar, although the means of that identification was not stated. The biopsy report was given as follows: "The pigment granules lie free in the corium and are surrounded by intense proliferation of connective tissue elements. The epidermis is markedly hypertrophied and actively proliferating. Cell nests are present. There is polymorphonuclear leukocytosis, both in the corium and the epidermis. There is no evidence of any infecting agent. The whole appearance is one of an epithelial papilloma, of doubtful malignancy, and should be allied to the condition of chimney sweep's carcinoma, and the carcinoma of paraffin workers. The causal agent is undoubtedly the pigment." However, Dr. Gray and Dr. O'Donovan expressed the view that the warty overgrowth was not of the nature of a carcinoma cutis, but rather that of lupus verrucosus.

Psychological implications of tattooing. A popular author, Hugh Garner[28] has described tattooing in the following words, "Among all the forms of mass masochism practised by that frailty known as man, none is quite as silly as the acquiring of tattoos. This egocentric perversion has had its devotees since the dawn of time, and in inverted sequence, it has been a tribal custom, penal stigma, class craze, snobbish adornment, and finally a vulgar affectation. Among the Maoris and various Hindoo sects it is still a mark of caste and beauty, but among most Western peoples, it is at best a juvenile indiscretion, and at worst a

thing of shame and loathing to those of us who are tattooed. It can, and does, slow a person's social life to a crawl." In his article he mentioned the late nineteenth century fad for tattooing, in which many members of royalty and the upper classes succumbed to the practice. "In 1893, the visiting Earl of Craven almost drowned his amazed fellow bathers in the pool of the New York Racquet Club when he appeared flaunting his uncovered tattoos." Apparently the most famous of the present day, are Betty Carstairs the racing driver, and King Frederick, IX, of Denmark.

The lively interest that the subject of tattoo still holds on the public is illustrated by the fact that articles have appeared in recent international popular magazines. For example, the English, "Punch", 5 August 1953, the Canadian "Saturday Night", 11 April 1953, and the American, "Holiday", June, 1953.

Motivation is a factor that has interested psychologists deeply, and they have used tattoo as a key in an effort to unlock deep and very fundamental behavior mechanisms. Bromberg[12] has had wide experience in this field. He has emphasized the impulsive nature of the desire to become tattooed, as if a great resistance had to be overcome. Included in that resistance factor were two thoughts, first the social taboo against tattoo, and secondly a subconscious unwillingness to injure the narcissistic organ, the skin. Often the impulsive nature of the act has been aided by the injudicious use of alcohol, by the "dares" or urgings of friends. He separated tattooed men into two groups. The first might be described as a collector, an older, more virile man, often a sailor, in whom the process was clearly an exhibitionistic one. At the extreme end of this group can be found the tattooed circus people. This type of overall tattooing has been seen at its best in work that has come from the Far East, and particularly Burma. The "Tattooed Man at Vienna"[39] is an editorial commentary in Lancet for 1872, describing a case of overall tattooing as presented at the clinic of Professor Hebra. This specimen had 388 designs on his body and looked as if his body, "from his forehead to his toes, was covered by a close-fitting, transparent shawl". Later he was imported to America by P. T. Barnum for his circus. An even earlier case was "Chambers, The Tattooed Canadian" as described by Gascoigne[27] in Lancet. The second group of Bromberg's contained the imitator or pretender, who desired to be identified with a stronger man. He also dealt with designs, the strongly heterosexual features of some, the anthropomorphic types of ships, horse, historical figures, and those indicating sadism such as skulls, blood and daggers. In this connection the masochistic nature of the tattoo process has significance. Mother fixation factors appeared in the designs concerning honor and guilt. The relationship of clothes to tattoos was an interesting angle brought out by Bromberg. He showed that connection by explaining the sudden attention of the adolescent boy to flashy clothes, and then the transfer of this to the body, by means of tattooing. He felt, however, that, contrary to the opinions of Lombroso[43] tattooing seemed to be a manifestation of neurotic conflict, depicted on the body surface, rather than an atavistic regression to a primitive love of adornment.

Both authors have commented upon the frequency of tattoos amongst criminals. Similar observations have been made by Pollak and McKenna[56] in a series of tattooed psychotic patients. Lander and Kohn[40] published certain observations in 1943, in which they

showed that the rejection rate for tattooed persons on induction into the Armed Forces was high, and mostly due to neuropsychiatric reasons.

That tattooing has an impulsive basis has also been shown by Simons[73] in his description of the tattooing done by British prisoners-of-war in a Japanese camp in Java during World War II. A sudden craze for tattooing developed about 3 months after capture, and reached epidemic proportions for the next 6 months, during which time most of the men under the age of 22 were tattooed by other inmates. Then as suddenly as the fad had started, it stopped.

It should be strongly emphasized that a large number of normal young men were tattooed during World War II. That a tattoo was often considered as a sort of fraternity pin to Navy men, no doubt was responsible for much of the tattooing. Other factors, such as the commonly expressed "just for the hell of it" attitude were present as well.

This brief discussion of some of the recent psychological views on tattooing has been given for interest and to serve as a prelude to what many people want to do with their tattoos, and that is, get them taken off.

METHODS OF REMOVAL. *Surgical.* The most satisfactory methods of removal of tattoos have proven to be the surgical excisions. Complete excision with subsequent skin grafting is the simplest procedure. The operation of serial excision, as used by Orr[53] in 1933, has been particularly useful with elongated designs and with locations where the skin is lax. A long slice of tattooed skin is removed in the long axis of the tattoo, with approximation of the edges and subcuticular suturing. Then after healing has taken place, the process is repeated, finally leaving only a long, fine scar.

Careful use of the dermatome has been fairly successful. A shallow setting is used so that the upper layers of skin are shaved off, leaving islands of epithelium to regenerate. Certain of the collections of pigment are actually removed with the separated part of the skin, and others, whose position has been visualized, can be teased away by dissection.

Chemical. Chemical methods relying on causing an acute inflammatory process in the vicinity of the tattoo, with subsequent shedding in its evolution to the surface, have been used with success but there have been many chemical scars caused.

Such methods dating back to antiquity have included preparations of witchcraft, such as garlic, decomposed urine, mother's milk, cantharides, lemon juice, strong vinegar, and others, as well as caustic and keratolytic groups of drugs.

Shie[71], in 1928, has described methods of removal thoroughly, especially the tannic acid-silver nitrate method of Variot[86], first reported in 1888. Briefly, to describe it, a 50% tannic acid solution is tattooed throughout the whole tattoo design, with the excess being washed off with water. The normal surrounding skin is protected with collodion, then the design is rubbed with a stick of silver nitrate. The area is then washed free with water, and a dry dressing applied. Within 2 to 3 weeks a slough separates leaving a new pink epithelium underneath. Occasionally a second treatment may be required.

A further method which gained considerable popularity in its day was the zinc chloride method, described by Brault[71] in 1895, in which a 75% solution of zinc chloride was tattooed into the skin, being careful to go only as far as the superficial part of the corium. This caused a similar slough to sepa-

rate, but often a granulating wound remained, with a resulting scar.

Many other procedures have had their proponents, but few have stood the test of time. Some were hydrogen peroxide in glycerine, strong phenol solutions followed by alcohol, local applications of strong acids, chlorine solutions, organic digestants and others.

Physical. Strakosch[75], in 1953, and Rosenberg[62], in 1952, described a sandpaper method for removing freckles and tattoos. This method, which has been used in different form before, consisted of the gentle rubbing of the design with a roll of fine sandpaper until the tattoo was obliterated. After healing the skin was pink, with fading occurring in 2 months. A warning against the injudicious or widespread use of this method was given.

The use of carbon dioxide snow has been advocated, as well as no less than the application of a red-hot iron.

Electrolytic methods were in vogue at one time, either in the form of direct dissection, or planned cauterization followed by extrusion of the pigment along with the slough.

TATTOO AS THERAPY. Therapeutic tattooing for the cosmetic improvement of capillary hemangioma has been described by Conway[17] in 1948. Such a procedure, using neutral or flesh colored pigments, has also been used as a means of obscuring an unwanted tattoo.

The use of mercury bisulfide, tattooed into the skin, as a way of ameliorating the irritation of intractable pruritus ani and vulvae has been reported by Turell[82], in 1948.

TATTOO AS IDENTIFICATION. The practice of using a tattoo as a means of identification has seen regular use throughout the years. In the British Army, distinguishing initials, such as B.C. (for bad character) were tattooed on repeated violators as late as 1870. Similarily in Italy and Spain, tattooing had a penal significance dating back to times when convicted felons were tattooed for identification. In World War II concentration camp inmates were marked by number tattooing and numerous other symbols were used by special units. Suggestions have been made to have blood groups or social security numbers tattooed on people. In conclusion, an enterprising surgeon has suggested that on completion of an operation the initials of the surgeon and the date should be tattooed on the skin near the incision in telegraphic code.

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PROCEEDINGS OF

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A Critical Study of "Inhibition" and "Facilitation" of Muscle Tone, by Means of Implanted Electrodes in the Anesthetized and Unanesthetized Cat. W. W. CHAMBERS, PH.D., AND J. M. SPRAGUE, PH.D. (Dept. Anat., Univ. of Penna.). Medullary reticular formation has been extensively stimulated directly by means of stereotaxically oriented electrodes, and indirectly by way of neuronal pathways from cerebellum, in anesthetized, unanesthetized and decerebrated cats. Predominant effect on postural tonus was a reciprocal one. Direct stimulation of medial reticular formation yielded a postural pattern of ipsilateral flexion, and extensor inhibition, and a contralateral extension, and flexor inhibition. Lateral reticular formation evoked a pattern opposite in direction to medial one. Indirect reticular stimulation from cerebellum also gave two postural patterns: one, related to vermal cortex and to fastigial nuclei, was identical with that evoked from medial reticular formation; the other, obtained from lateral cortex of anterior lobe and paramedial lobule and from interpositus nuclei, was similar to that from lateral reticular formation. Reticular patterns persisted unchanged after removal of cerebellum. Stimulation of medullary reticular formation through chronically implanted electrodes revealed in the unanesthetized and freely moving animal a number of well organized and complicated movements of whole body. The entire postural substratum of sleep was produced from one medial reticular point: lowering of head, circling, lying down and curling up in a position typical of feline sleep. Generalized non-reciprocal inhibition and facilitation commonly ascribed to medial and lateral reticular areas were never found in the unanesthetized animal. They were much less frequent than were reciprocal postural patterns in the decerebrated animal and in some preparations were not found at all. They were relatively more numerous in those preparations which were depressed reflexly, and were in most cases obtained at stimulus intensities two to three times threshold strength, the threshold response having been reciprocal. These results implicate the medullary reticular formations and cerebellum in basic reciprocal control of posture found elsewhere, and suggest that the concept of general inhibition and facilitations is valid only under special conditions.

Paper Chromatographic Studies of the Excretion of Adrenal Cortical Hormones. F. C. DOHAN, M.D., E. M. RICHARDSON, PH.D., J. C. TOUCHSTONE, PH.D., HELEN BULASCHENKO, M.S., AND IRMGAARD LANDOLT, B.S. (William Pepper Laboratory of Clinical Medicine, Hospital of the University of Pennsylvania). Analyses were made of major specific alpha-ketolic steroid metabolites found in urine after oral administration of hydrocortisone ("F"), cortisone ("E"), 11-desoxy-17-hydroxycorticosterone ("S"), corticosterone ("B"), 11-dehydrocorticosterone ("A"), and 11-desoxycorticosterone ("DOC") to individuals with severe adrenal cortical insufficiency. Urine was collected for 24 hours or longer. Following hy-

drolysis by glucuronidase and acid, the steroid metabolites were extracted with chloroform, and separated by the paper chromatographic procedure of Burton, Zaffaroni, and Keutmann. The position of the alpha-ketolic metabolites was determined by spraying chromatograms with blue tetrazolium, and densities were read directly from the paper strip in a Beckman spectrophotometer. Eluates were made of appropriate sections of duplicate chromatograms and further separation effected. Identification studies included running rates in various solvent systems as the alcohol and the acetate and reaction with phenylhydrazine, the Pettenkoffer reaction, absorption spectra in concentrated sulfuric acid, and in seven instances, infra-red spectrographic analysis, done through the courtesy of Dr. Thomas Gallagher.

Results. The tetrahydro derivative of all six compounds was found in relatively large amounts in the urinary extract after administration of the parent compound, indicating that reduction in ring A is one of the major pathways for the formation of alpha-ketolic metabolites. In addition, interconvertibility of the hydroxyl and ketone substituents at carbon atom 11 was demonstrated for cortisone and hydrocortisone and for corticosterone and 11-dehydrocorticosterone, by the finding of the transformation product and its tetrahydro derivative in urinary extracts.

Approximately 0.7 to 2.5 mg. of alpha-ketolic steroids per 24 hours was extracted from urine of normal individuals. After intravenous ACTH, there was an increase up to 15 times the amount found prior to injection. The chromatographic pattern of alpha-ketolic steroids of normal individuals (before and after ACTH) suggests that cortisone or hydrocortisone is the chief adrenal secretory product, and that corticosterone (or possibly 11-dehydrocorticosterone, and perhaps other alpha-ketols) are also secreted.

The Mechanism of Action of Glyceraldehyde-3-phosphate Dehydrogenase. PETER OESPER, PH.D. (Division of Biological Chemistry, Hahnemann Medical College, Philadelphia, Pa.). The glyceraldehyde-3-phosphate dehydrogenases of both yeast and muscle catalyze the exchange of phosphate between inorganic phosphate and the 1-position of 1,3-diphosphoglyceric acid. The yeast enzyme also catalyzes the arsenolysis of 1,3-diphosphoglyceric acid to 3-phosphoglyceric acid. These reactions do not proceed by reduction of the diphosphoglyceric acid to glyceraldehyde-3-phosphate, and subsequent reoxidation. These data support the theory that the initial step in the conversion of glyceraldehyde-3-phosphate to 1,3-diphosphoglyceric acid is an oxidation, rather than an uptake of phosphate. This work will be reported in detail in the Journal of Biological Chemistry.

The Effect of Bulbocapnine upon the Spontaneous Electric Activity of the Brain and its Reactivity to Afferent Stimuli. E. G. SZEKELY, V.M.D., AND E. A. SPIEGEL, M.D. (Department of Experimental Neurology, Temple University School of Medicine). In cataplexy-producing doses, bulbocapnine has a slight depressive effect upon the electric activity of the cerebrum that may be detected in the prosencephalon, diencephalon and mesencephalon. It affects chiefly the fast activity. Only occasionally slow waves or transitory excitatory states were seen with the doses used. In the cataleptic state, the reactivity of the cortex and various subcortical areas (hypothalamus, reticulate substance of the midbrain, cerebellar cortex) to afferent impulses is preserved, or even increased. Simultaneous recordings from cortex and various subcortical areas reveal rather variable differences in the degree in which these regions may be affected, indicating that some degree of independence of the functional states of these regions may exist.

BOOK REVIEWS AND NOTICES

MURDER, MADNESS AND THE LAW. By LOUIS H. COHEN, M.D. Pp. 173. Cleveland: The World Publishing Co., 1952. Price, $3.50.

THIS is an excellent presentation by a psychiatrist with much legal experience of the manifold problems that arise in the trial and disposition of psychotic murderers. Illustrated by 17 appropriate cases, this little volume shows the difficulties and the shortcomings in present procedure and offers some practical advice to those concerned with this field. Not only physicians, psychiatrists and members of the legal profession, but any interested layman will find here the answers to some very practical questions. R. K.

DRUG ADDICTION AMONG ADOLESCENTS. Pp. 320. New York: Blakiston Co., 1953. Price, $4.00.

THIS is a well printed and arranged report of two conferences on Drug Addition among adolescents which occurred in 1951 and 1952 and were sponsored by the New York Academy of Medicine. Fifty-two distinguished men and women participated in these panels. The nature, etiology, prognosis and treatment of drug habituation and/or addiction are discussed in great detail in this volume. It was stressed by many speakers that narcotic addiction is not a disease but really a symptom of a psychological imbalance or some antisocial or amoral state; hence the reason for almost certain relapse after treatment because the symptom and not the disease was treated. The role of the Courts in handling this problem as compared with that of the physician was discussed.

The reviewer of this volume cannot avoid remarking on the senseless futility of a suggestion by a discussant that to require a physician's prescription for the sale of every hypodermic syringe would lessen drug addiction. The greatest difficulty in the treatment of pre-adult and adult addicts, it was stated, is not found in the immediate detoxification but in the later rehabilitation of the patient. With this statement the reviewer heartily concurs. The problems encountered in the detection and treatment of the adolescent addict are in some ways less troublesome than in the adult. Prevention is in the case of the former more often possible than in the latter. After all it was repeatedly stressed by those participating in this panel that no one knows either the extent of adolescent addiction or the real reason for its thousands of victims.

This book is a very informative addition to the literature on narcotic addiction (including marijuana and cocaine). The great value of this conference in the opinion of the reviewer lies in the possibility that young habitues can be prevented from becoming criminal addicts for whose rehabilitation there is little if any hope. J. D.

THE WORK OF WHO, 1951. ANNUAL REPORT OF THE DIRECTOR-GENERAL TO THE WORLD HEALTH ASSEMBLY AND TO THE UNITED NATIONS. Pp. 200; maps and 16 pages of illustrations. Geneva: World Health Organization, 1952. Price, $1.25.

A CONCISE interesting record of achievement in a field that has done most to promote world unification and the mutual understanding of the nations: the World Health Organization under the able leadership of Doctor Chisholm. R. K.

SURGICAL FORUM CLINICAL CONGRESS OF THE AMERICAN COLLEGE OF SURGEONS 1952. Edited by OWEN H. WANGENSTEEN. Pp. 716; 267 ills. Philadelphia: W. B. Saunders Co., 1953. Price, $10.00.

THIS volume contains the papers presented at the Forum on Fundamental Surgical Problems which is an outstanding part of the program of the annual meeting of the American College of Surgeons. These papers were presented at the New York City meeting in September of 1952. The papers are grouped under the particular field to which they apply. Thus they are divided into those on the stomach; heart and great vessels; heart and blood circulation; gynecology, obstetrics and anesthesia; lungs and liver; shock; portal hypertension, liver, pancreas and blood coagulation; water balance and electrolytes; plastic surgery; thermal injuries and cancer. The papers represent work which is primarily of a clinical investigative nature both in the laboratory and on the patient. All of the papers have been condensed and thus make for attractive and interesting reading. It is a book of real value, not only to those interested in the field of surgery, but it also has

much of interest to any one who has a desire to know of the investigative work being carried out in the various laboratories and clinics throughout the nation.

The printing makes for easy reading and the illustrations are adequate. H. C.

COMROE'S ARTHRITIS AND ALLIED CONDITIONS. Edited by JOSEPH LEE HOLLANDER, M.D. 5th ed. Pp. 1103; 399 ills. Philadelphia: Lea & Febiger, 1953. Price, $16.00.

THE profession will welcome the new fifth edition of this authoritative work. Under the editorship of Doctor Hollander, the 16 contributors, all of them specialists in the field of rheumatic diseases, have brought the subject matter thoroughly up-to-date. The rapid and important changes in the field have necessitated complete re-writing of some sections, the addition of new ones and important rearrangements. Throughout the interest of the practicing physician has been kept in mind since he will use it largely as a reference book. At the same time, the numerous references to the literature have been retained, and increased by new material for the special student of the subject. The work is highly recommended. R. K.

MEDICINE. VOLUME I. THE PATIENT AND HIS DISEASE. By A. E. CLARK-KENNEDY, M.D., AMERICAN COLLEGE OF SURGEONS, 1952. and Dean of the Medical School. 2nd ed. Pp. 410. London: E. & S. Livingstone, Ltd., 1953. Price, $6.00.

THIS is not simply another textbook in Medicine; nor is it a compilation of data or a symposium of disconnected subjects by a panel of authors. It is a philosophical approach, an attempt to deal with fundamental principles rather than with the details of medical practice, by one who is both an experienced teacher of physiology and clinical medicine as well as the Dean of a medical school. The author has succeeded admirably in writing a book that gives viewpoints rather than isolated facts, that challenges to thought rather than courts memorizing. Under the subtitle, The Patient and His Disease, this first volume has chapters on Body and Mind, Symptoms, Symptoms and Signs, Heredity and Environment, The Nature of Disease. (The second volume, not here reviewed, deals with Diagnosis, Prevention and Treatment.) Written for the medical reader regardless of the stage of his career, it should be helpful to all physicians as well as students. R. K.

DIAGNOSTIC TESTS IN NEUROLOGY. A SELECTION FOR OFFICE USE. By ROBERT WARTENBERG, M.D., Professor of Neurology, University of California. Pp. 228; 62 ills. Chicago: Year Book Publishers Inc., 1953. Price, $4.50.

This book is truly one that deserves commendation. I feel sure that students of neurology will find in it things which they can find nowhere else. It is a very detailed and yet simple description of the various tests worked out by the author and others. It is simple enough that everyone can understand it and no one can misinterpret it. I am sure that anyone even remotely interested in neurology will find it stimulating, informative, and interesting. It is, moreover, well illustrated. There are certain places where, perhaps, a little change might be for the better, such as: page 86, where mention is made of the nerve twig going from the radial nerve to the brachioradialis muscle. Perhaps mention of where this entry takes place would be a valuable addition. It seems to the reviewer too that some of the tests described are merely mild variations of others. In speaking of the snout reflex and other similar related reflexes, no mention is made of the hard palate reflex.

One cannot read this book without commenting on the author's preface or introduction. Most certainly he is correct when he F.R.C.P., Physician to the London Hospital rely too much on the laboratory side of the examination and too little on the physical examination including, in particular, simple inspection of the patient.

In summary, therefore, the reviewer feels that this book is a very fine supplement to the clinical textbook of neurology, and, while he would not go so far as to say it should be in every medical student's hands, the student should know of this book, and those interested certainly should be urged to purchase it. S. G.

DIFFERENTIALDIAGNOSE INNERE KRANKHEITEN. By DR. ROBERT HEGGLIN, Univ. of Zurich. 2nd ed. Pp. 556; 250 ills. Stuttgart: Georg Thieme Verlag, 1953. Price, DM 55.

THIS is an interesting, concise and practical book on the differential diagnosis of internal diseases. The material is arranged under disease manifestation headings, followed by discussions of the possible causes. The headings

include The Anemias, Hemorrhagic Diatheses, The Febrile State, Headache, Dyspnea, Cardiac Arrhythmias, Electrocardiographic Abnormalities, Cyanosis, Chest Pain, Hypertension, Hypotension, Pulmonary Shadows, Hilus Enlargement, Abdominal Pain, The Diarrheas, Icterus, Splenomegaly, Hematuria, Albuminuria, Pyuria, Cylindruria, The Edemas, Pains in the Extremities and in the Spine, and Unconsciousness. The material is very well presented and adequately illustrated. The popularity of the work may be judged from the fact that the first edition was exhausted within a year. The new edition differs chiefly by the addition of two chapters, those on Headache and Pain in the Extremities. The book is recommended to all who read German. R. K.

SECTIONAL RADIOGRAPHY OF THE CHEST. BY IRVING J. KANE, M.D., Consultant in Chest Diseases, U. S. Naval Hospital, St. Albans, New York. Pp. 154; 101 ills. New York: Springer Publishing Co., 1953. Price, $7.50.

DOCTOR KANE'S enthusiasm for sectional radiography is imparted to the reader. After reading the book one feels that planigraphy is generally not being utilized to its fullest advantage. The simpleness of the procedure and its adaptability to ordinary Roentgen-ray machines is emphasized. The indications are thoroughly discussed. Its utilization, in cases where signs or symptoms point toward chest disease, despite a normal conventional roentgenogram, is considered the most important indication. Its usefulness in evaluation of shadows of uncertain nature and in discovering associated lesions is well demonstrated. This is an excellent book, written in clear fashion and profusely illustrated. It discloses how much information may be obtained by the proper understanding and use of the method. H. W.

DIE ZUSAMMENARBEIT DES GEBURTSHELFERS, DES KINDERARZTES UND DES SEROLOGEN BEI DER PROPHYLAXE UND THERAPIE DES NEUGEBORENEN-ERYTHROBLASTOSE. BY PROF. DR. P. DAHR, PROF. DR. K. H. SCHAFER AND PRIV.-DOZ. DR. A. STADTMULLER. Pp. 64; 10 ills. Stuttgart: Georg Thieme Verlag, 1953 (Agents for U. S., Grune & Stratton, New York). Price, DM 5.70.

THE relation of neonatal erythroblastosis to the Rh factor was discovered in the United States during the time of World War II, so that this knowledge became available to the German profession sometime after that conflict. The present brochure is intended to make available diagnostic principles and therapeutic procedures in this condition through the collaboration of the obstetrician, pediatrician and the serologist. R. K.

MAN'S BACK. BY THEODORE A. WILLIS, M.D., Formerly Head, Dept. of Orthopedic Surgery, St. Luke's Hospital, Cleveland. Pp. 170; 210 ills. Springfield, Ill.: Charles C Thomas, 1953. Price, $9.50.

I have had the opportunity of studying Dr. Willis's treatise on the back and have edited each chapter carefully and in considerable detail. I consider this one of the finest contributions to the subject and feel that it can be employed in undergraduate and graduate teaching to an unlimited degree. Certain chapters stand out especially and I am referring particularly to Embryology of the Back, Anatomy of the Back, Vertebral Anomalies and Defects of Development, Mechanics of the Back, Examination of the Back, and Physical Therapy of Back Lesions. The reviewer at first was somewhat annoyed by the absence of a bibliography and the omission of personal names relating to the various contributions. However, the personal experience of Dr. Willis, his depth of vision, his knowledge of embryology, anatomy and medicine in general, generously overcomes such criticism.

I wish to thank Dr. Willis personally for his most interesting and instructive contribution and sincerely hope that others will duplicate my experience. J. M.

MEDICAL CLINICS OF NORTH AMERICA, JULY, 1953. Nationwide Symposium on Bedside Management. Pp. 329; 35 ills. Philadelphia: W. B. Saunders Co., 1953. Price, $16.00 per annum.

UNDER the editorship of Dr. Wohl, 36 contributors from many parts of the country have prepared 20 articles on various aspects of Bedside Management. They include such topics as The Management of Cardiac Emergencies, The Treatment of Cardiac Decompensation, Arterial Hypertension, Bronchial Asthma, Bronchiectasis, Pneumonia, Goiter, Amenorrhea, Diabetes, Thrombophlebitis and Phlebothrombosis, Acute Burns, Nephritis, Liver Disease, Ulcerative Colitis, Common Skin Diseases, Anemias, Backache, Rheumatic Fever, Rheumatoid Arthritis and Headache. Surely every physician should be able to

find something of interest and much that is useful. R. K.

THERAPEUTICS IN INTERNAL MEDICINE. Edited by FRANKLIN A. KYSER, M.D. 2nd ed. Pp. 830. New York: Paul B. Hoeber, 1953. Price, $15.00.

THIS book is a practical, concise presentation of the treatment of internal diseases. Under the editorship of Dr. Kyser, 84 recognized authorities have written the volume, including seventeen new contributors of 12 new sections in this, the second edition. In addition to the treatment itself, there are discussed, whenever necessary, the physiologic, etiologic and pathologic principles that underlie the treatment. There are also sections on the common neurologic and dermatologic disorders encountered in internal medicine. The book should find a very favorable reception. R. K.

BACK DOWN THE RIDGE. By W. L. WHITE. Pp. 182. New York: Harcourt, Brace & Co., 1953. Price, $3.00.

A report for popular consumption of the manner and the results of the handling of battle casualties in the Armed Forces in Korea. The excellence of those results, far beyond those of any previous war, and the fascinating style of the writer combine to make this acceptable as well as interesting reading. R. K.

CLASSICS IN CLINICAL DERMATOLOGY WITH BIOGRAPHICAL SKETCHES. By WALTER B. SHELLEY, M.D., Ph.D., Assoc. Professor of Dermatology and Syphilology, University of Pennsylvania; and JOHN T. CRISSEY, M.D., Instructor in Dermatology, University of Pennsylvania. Pp. 467; 107 ills. Springfield, Ill.: Charles C Thomas, 1953. Price, $10.50.

Shelley and Crissey's CLASSICS IN CLINICAL DERMATOLOGY, is, as Stokes states in the introduction, "the comparative novelty of an effort on the part of the young investigators to re-discover for themselves and for us the genealogy of the dermatologic discipline." It is a good book and fills a need for the edification of the student in dermatology who should have knowledge of the contributions of the pioneer clinicians in this field. It contains a short biography of a selected group of 95 men and original descriptions, or the authors' translations of the descriptions, of 143 diseases. These diseases are both rarities and common clinic fare. The translations of the German and French descriptions are good and the photographs as satisfactory as one could hope for. The only real deficiency in this volume is an occasional lack of correlation of certain data. For example, to the uninitiated, the description by White, on page 225, in "A Golden Age" of keratosis follicularis, would seem to be a different disease from that described by Darier within a few months of White's description (page 398) under "More Recent Observations." Both descriptions were published in 1889. One might also wish for slightly larger biographies, but the volume is an excellent start. H. B.

MALARIA TERMINOLOGY. By SIR GORDON COVELL, P. F. RUSSELL AND N. H. SWELLENGREBEL. Pp. 82. Geneva: World Health Organization, 1953. Price, $1.00.

A uniform terminology is a basic necessity in the recording and dissemination of any form of knowledge. The World Health Organization is to be commended for having brought thoroughly up-to-date an earlier compilation of accepted terms in the field of malariology, that of 1940 by the Malaria Commission of the League of Nations. R. K.

GOUT AND GOUTY ARTHRITIS. By JOHN M. TALBOTT, M.D., Professor of Medicine, University of Buffalo. Pp. 89; 32 ills. New New York: Grune & Stratton, 1953. Price, $4.00.

DR. TALBOTT, who is well qualified to write this book, presents an excellent summary of our present knowledge of the gouty state and of gouty arthritis. The book is written from the viewpoint of the clinician. It gives all essentials of the diagnosis and management of gout and evaluates, in the perspective of the author's experience, both new and older remedies. In addition, there is a valuable discussion of recent knowledge of the underlying physiologic disturbances in the gouty state. The book will well serve the needs of the general internist, and the general practitioner; it also provides a good source of reference for the rheumatologist. J. L.

THEORIE UND PRAXIS DER MEDIZINISCHEN FORSCHUNG. By DR. KARL KISSKALT. 3rd ed. Pp. 270. Wiesbaden: Verlag für Angewandte Wissenchaften, 1953. Price, DM 15.80.

IN the preface to the first edition the author points out that no other science pos-

sesses so many books that deal with methodology. They describe how to make manual and instrumental examinations but they have little or nothing to say about the mental processes of research. This fact stimulated the author to write an interesting book that has now reached its third edition. All who are engaged in research and who can read German will find here much that is useful and challenging. It is particularly recommended to young men embarking on research careers. R. K.

BASIC BACTERIOLOGY; ITS BIOLOGICAL AND CHEMICAL BACKGROUND. By CARL LAMANNA, Ph.D., and M. FRANK MALLETTE, Ph.D., The Johns Hopkins University School of Hygiene and Public Health. Pp. 677; 100 ills., 66 tables. Baltimore: Williams & Wilkins Co., 1953. Price, $10.00.

THE fourteen well-documented chapters and appendix in this book on bacterial physiology bring the past up to the present and reflect into the future. The following chapter headings suggest the nature of the material included: Dyes and Staining; Surface Properties of Bacteria; Enzymes of Bacteria; Physical Factors Affecting Bacteria; The Variation and Genetics of Bacteria; Bacterial Metabolism; Chemical Disinfection.

In the handling of these subjects covering bacterial morphology, physiology, taxonomy, variation, heredity and evolution, the authors, well qualified in their respective fields, have filled a definite need in a book that fits into that area between the elementary and advanced in relation to intimate unicellular phenomena. It is not, however, an elementary book. By more detailed discussion of factual data the authors make one, with a knowledge of chemistry and physics, feel familiar with complex physiological phenomena. This treatment of bacterial physiology should be welcomed by the student, teacher and specialist in bacteriology. T. A.

THE NATURAL HISTORY OF INFECTIOUS DISEASE. By SIR MACFARLANE BURNET, M.D., F.R.S. 2nd ed. Pp. 356; 12 ills. New York: Cambridge University Press, 1953. Price, $4.50.

THIS is a book on the nature, causes, manner of spread and methods of control of infectious diseases; with a more detailed discussion of diphtheria, influenza, tuberculosis, plague, cholera, malaria, yellow fever, by a recognized authority in the field. Since the first editon appeared in 1940, there have been great advances, especially in treatment, so that a new chapter on Antibacterial Drugs has been added. The emphasis is on basic principles rather than on clinical details. The book is written in a simple, clear style, with the lay reader, interested in health work, in mind. R. K.

PERSONALITY MANIFESTATIONS IN PSYCHOSOMATIC ILLNESS. VISUAL AID CHARTS TO PSYCHOTHERAPY. By O. SPURGEON ENGLISH, M.D., Chairman, Department of Psychiatry, Temple University Medical School and Hospital. Pp. 57; 10 ills. Philadelphia: Edward Stern and Co., Inc., 1953. Price, $1.00.

THE problem of explaining to patients that symptoms are of emotional origin often presents difficulties. Dr. English designed a series of colored charts which help the physician to do this. He emphasizes that they are not a substitute for psychotherapy but merely an aid to permit the patient to understand the interaction between the emotions and bodily disturbances. Ten plates, illustrating a number of psychosomatic disorders, accompanied by some textual material and illustrative case reports, make up a small book which should prove very useful to the general physician. E. W.

STRESS INCONTINENCE IN THE FEMALE. By JOHN C. ULLERY, M.D., F.A.C.S., F.I.C.S., Asst. Prof. Obstetrics and Gynecology, Jefferson Medical College; Obstetrician and Gynecologist, Pennsylvania Hospital. Pp. 149; 82 ills., some in color. New York: Grune & Stratton, 1953. Price, $6.75.

THE author has been highly successful in his attempt to correlate the mass of information concerning etiology, investigation and treatment in women with inadequacies of urinary control. Embryology and anatomy of the bladder and urethra and the physiology of urination and continence are discussed and the many methods for evaluating and treating women with incontinence are presented. Operative procedures are described in detail and the steps in the performance of the more important ones are illustrated.

The fact that Dr. Ullery has more than a passing interest in disorders of micturition in the female and has had considerable experience in their correction makes the information presented far more valuable and practical, because in addition to presenting the material, he makes an attempt to evaluate

each procedure in the light of his personal experiences with it.

This monograph should be particularly valuable to gynecologists and surgeons who must correct the lesions but it should also receive the attention of those who are responsible for care during pregnancy and delivery because at that time preventive measures, which also are discussed, may be instituted. J. W.

THE BOOK OF HEALTH. Compiled and edited by RANDOLPH LEE CLARK, JR., M.D., M.Sc. (SURGERY), Director and Surgeon-in-Chief, University of Texas M. D. Anderson Hospital and RUSSELL W. CUMLEY, Ph.D., Director of Publications, University of Texas. Pp. 770; 1400 ills. New York: Elsevier Press, 1953. Price, $10.00.

THIS is the modern version of the "doctor book" of a former generation. But it is a much more sophisticated, accurate and useful volume than the ones that were found in many homes of a generation ago. This is really a bird's-eye view of medical history and medical knowledge as set forth by 242 contributors and splendidly edited and compiled. It should prove interesting, stimulating and informative to all laymen but particularly to young men and women who are thinking of a career in medicine, dentistry, nursing and allied branches of healing. There are numerous excellent illustrations.

R. K.

MODERN CLINICAL PSYCHIATRY. BY ARTHUR P. NOYES, M.D., Supt., Norristown State Hospital. 4th ed. Pp. 609. Philadelphia: W. B. Saunders Co., 1953. Price $7.00.

THIS fourth edition of an already popular textbook on psychiatry has been revised and expanded in various areas. The presentation of genetic and dynamic concepts is more complete. There is a fuller exposition on group therapy. The classification follows the most therapy. The classification follows the most recent changes made by the American Psychiatric Association and it makes an excellent textbook for students, residents and anyone wishing a complete presentation of psychiatric disease and its treatment. O. E.

DIE ZUCKERKRANKHEIT. BY PROF. DR. ERNST WIECHMANN. Pp. 318. Munich: J. F. Lehmanns Verlag, 1953. Price, DM 26.00.

DR. WIECHMANN'S avowed intention that this book should serve the needs of the medical student, the physician in general practice and in various specialties is well fulfilled. This book is the outgrowth of many years of research by the author and practical work in the diabetic clinic of Professor Friedrich Moritz of Cologne, Germany.

The first 20 pages of the book deal with carbohydrate metabolism and the prevailing concepts of the etiology of diabetes mellitus.

The major section of the book deals with diagnosis, complications and treatment of the disease. The specialist will find of particular interest a short but concise and useful description of the role of diabetes mellitus in his respective field of endeavor.

The book presents well documented facts. The text is clear and smoothly written. The bibliography is arranged by chapters and includes only the most important contributions to the field. The index is quite adequate.

The book can be recommended as an accurate and up-to-date summary of an important subject of particular interest to those who read German. M. W.

FRAZER'S MANUAL OF EMBRYOLOGY. BY J. S. BAXTER, M.A., M.Sc., M.D., F.R.C.S.I. Professor of Anatomy, University College, Cardiff. 3rd ed. Pp. 488; 287 ills. London: Balliere, Tindall & Cox, Ltd., 1953. (Williams & Wilkins Co., Baltimore, U.S. Agents). Price, $8.00.

Dr. Baxter has done an excellent job in the revision of this unique manual of embryology, retaining Professor Frazer's original plan.

The book is divided into two sections. The first covers the early embryology; the second, the development of regions. The description of the early embryology is the most complete the reviewer has encountered, but even so the most recent work on the segmenting human ova is not included (see Hertig, Rock, *et al.*, Anat. Rec. **112**, 40, 1952).

Although the text is well written and excellently illustrated, its organization is vastly different and its contents include innumerable details not usually encountered in our better known texts of Human Embryology.

Certain statements presented throughout the manual are contrary to our usual interpretation. For example, on page 25 one finds, "The placenta, . . . , is attached to the mucous lining of the uterus." This expression infers that the placenta is entirely of fetal origin. Such statements, although accurately handled in the subsequent discussion, are confusing to the student and should be reworded. . Anomalies are not considered.

Finally, one cannot help but criticise the lack of usage of proper anatomical descriptive terms. The words "back", "below", "above", and others, are used repeatedly, ofttimes in a very confusing manner. D. K.

OPERATIVE SURGERY. By GUY W. HORSLEY, B.S., M.D., F.A.C.S., Assoc. Prof. of Surgery, Med. College of Virginia, and ISAAC A. BIGGER, M.D., F.A.C.S., Prof. of Surgery, Medical College of Virginia. 6th ed. 2 vols. Pp. 1616; 1274 ills. St. Louis: C. V. Mosby Co., 1953. Price, $30.00.

THE sixth edition of *Operative Surgery* has been ably assembled by Doctors Horsley and Bigger. They have associated themselves with qualified men in allied surgical specialties, thus increasing markedly the scope of this work, the first edition of which appeared in 1921 and which was for the most part a description of operations used and recommended by Dr. J. Shelton Horsley. This edition appears in two volumes, containing about 750 pages each. There are 1274 excellent illustrations. For the most part the work describes one or two operations well rather than attempting to discuss various techniques. This practical and very sufficient work should prove invaluable to the young surgeon with a varied practice. G. R.

MODERN CONCEPTS IN MEDICINE. By JULIUS JENSEN, PH.D., M.R.C.S., L.R.C.P. Pp. 636. St. Louis: C. V. Mosby Co., 1953. Price, $11.50.

THE author of this volume has been greatly impressed by what he has considered to be inconsistencies in medical teaching. Also he has been much impressed by the writings of Selye, Wiener and Whyte, and has decided that the inconsistencies may be ironed out, in part at least, by teaching internal medicine within a framework derived from these writings and the ideas expressed therein.

Actually what the reviewer found was a series of disease descriptions written in an entirely traditional style and far too brief for the use of even a medical student. The gesture to the new scheme is found in the chapter headings and in the brief introductions which do suggest in a very general way the importance of disturbances of adaptation, cybernetics, and so forth. Why the author has not seized the opportunity to drive his points home by using the diseases themselves as illustrations (as Wiener, for example, has done so magnificently) the reviewer cannot fathom. It is his opinion that those who have read the original writings of Selye, Wiener and Whyte will find this book a disappointing anticlimax, and those who have not, had far better go to the originals. T. D.

ORAL HISTOLOGY AND EMBRYOLOGY. Edited by BALINT ORBAN, Loyola Univ. School of Dentistry. 3rd ed. Pp. 364; 263 ills., including 4 color plates. St. Louis: C. V. Mosby Co., 1953. Price, $8.50.

THE contributors to this excellent book have approached the subject of Oral Histology and Embryology with a continuity that is not only easy to read and understand for student and practitioner alike, but follows a pattern of uniformity, covering essential material only. It is especially interesting to observe that in spite of a thorough approach to the Development and Growth of the Teeth in the beginning of the book a short review of the developmental processes precede each succeeding chapter. This helps to familiarize the student once again with the importance of understanding fundamentals. Since the basic sciences play such an important role in student education the inclusion of histophysiologic and clinical considerations throughout the text serve as a continued reminder that one cannot be divorced from the other. In future editions of this work it might be better to reposition Chapters X and IX respectively to follow Chapter II as I find it more logical to teach in this order. Apart from this point the book deserves the highest recommendation for simplicity and accuracy of detail. F. J.

SURGICAL TECHNIQUE AND PRINCIPLES OF OPERATIVE SURGERY. By A. V. PARTIPILO, M.D., F.A.C.S., Assoc. Clin. Prof. of Surgery, Stritch School of Medicine of Loyola University. 5th ed. Pp. 694; 998 ills. Philadelphia: Lea & Febiger, 1953. Price, $15.00.

DOCTOR PARTIPILO was aided in this work by a number of prominent contributors. The book appears as one volume. The portions of the book written by Doctor Partipilo are complete, concise and very well done. The book stresses physiological principles. Some of the other portions of the text, although well-written, do not go into enough detail to warrant being included under the title of "Surgical Technique." Certain portions of the book tend to mention procedures rather

than to describe them. As a manual of surgical technique, this book must be considered somewhat deficient. G. R.

CARDIAC EMERGENCIES AND HEART FAILURE. PREVENTION AND TREATMENT. By ARTHUR M. MASTER, M.D., Cardiologist, Mount Sinai Hospital, New York; MARVIN MOSER, M.D., Former Fellow Cardiology, Mount Sinai Hospital; and HARRY L. JAFFE, M.D., Adjunct Physician, Cardiology, Mount Sinai Hospital. Pp. 159; 13 ills. Philadelphia: Lea & Febiger, 1952. Price, $3.00.

THE importance of the subjects discussed in this volume to the general practitioner is so great that the authors are to be congratulated on having recognized the need, and on having produced a concise, authoritative discussion, worthy of thorough study and digestion by all who cannot confess to complete mastery of such important knowledge. There is no intent on the part of the writers to provide a book on Cardiology, Radiology or Electrocardiography, but they have selected from these fields most of that which is pertinent. There has been excellent utilization of case histories as illustrative material. An excellent bibliography containing 280 references is appended for those desiring to delve further into basic physiology, pathology, and others.

A few omissions, considered by the reviewer to be of importance, might be worthy of mention. Perhaps the most serious of these concerns the dangers involved in the use of intravenous Pronestyl. The safer, yet speedily effective, intramuscular route is not mentioned, nor is there any statement concerning the importance of frequent blood pressure determinations. Whiskey is mentioned as being occasionally effective in angina, but without the warning, based on recent evidence, that this may be only the removal of the danger signal without any effect on the myocardial ischemia. More discussion of pulmonary embolism would seem to be warranted, particularly from the standpoint of prevention and treatment other than anticoagulants. Inasmuch as the inclusion of the management of the "ball valve" thrombus case is considered important enough for inclusion, it would seem also very much indicated to discuss air embolism, particularly since the therapy for the pulmonary, or venous, form is effective and should be more widely known. Perhaps the authors will consider these additions warranted in subsequent editions of the book. They are relatively minor points and do not detract from the value of the book as a whole, a book which can be heartily recommended to all medical students, interns and general practitioners. T. D.

TEXTBOOK OF PATHOLOGY. By WILLIAM BOYD, M.D., Prof. of Pathology, Univ. of British Columbia. 6th ed. Pp. 1024; 570 ills., 32 color plates. Philadelphia: Lea & Febiger, 1953. Price, $12.50.

DR. BOYD'S textbook of pathology is as familiar to the average American or Canadian medical man as his own prescription blank. For over 20 years it has been the most widely used text for students and reference for physicians in the field of pathology. To keep it modern Dr. Boyd has made five revisions. The last is probably the most extensive. The preface contains a full page listing of the changes and editions. The book is written in the same inimitable style and has the same sensible and lucid arrangement. The popularity of this text will almost surely be increased to new records by this last revision. E. A.

CLINICAL PROGRESS IN CARDIOVASCULAR DISEASE. Edited by HERRMAN L. BLUMGART, M.D., Physician-in-Chief, Beth Israel Hospital, and Professor of Medicine, Harvard Medical School. Pp. 143; 9 ills. New York: Grune & Stratton, 1952. Price, $4.50.

THE very rapid advances in the understanding of cardiovascular physiology and pathophysiology have been so rapid and have involved so wide a field of basic science disciplines that it has been extremely difficult for the cardiologist and internist to keep themselves informed, and to judge accurately what is justifiably and safely applicable to the care of patients. The Editorial Boards of Circulation and the American Heart Journal have wisely attempted to meet this need by publishing authoritative and critical Clinical Progress and Review articles. The volume edited by Dr. Blumgart is made up of selections from such articles in the former journal, and the result has been a book which will provide the physician with a large amount of very important material, condensed so that it may be read rapidly, and yet embracing all of the salient material needed to keep abreast of progress in the important selected subjects. Fifteen authorities have contributed, and the subjects include Atherosclerosis (a symposium covering experimental atherosclerosis, the human disease and diet, and the newer knowledge of the relationship of blood

lipids), The Management of Acute Cardiac Emergencies, Surgery for Mitral Stenosis, The Management of Cardiac Patients in Relation to Surgery, and Emotion and the Circulation. All cardiologists and internists will find this book very profitable reading. T. D.

WORLD DIRECTORY OF MEDICAL SCHOOLS. WORLD HEALTH ORGANIZATION. Pp. 220. Geneva: World Health Organization, 1953. Price, $4.00. (Distributed in U. S. by Columbia Univ. Press, New York.)

THIS tabular presentation of information on over 500 world medical schools gives, when known: 1) name and location of school, 2) founding date, 3) administering body, 4) academic year, 5) admission requirements, 6) size of faculty, 7) total enrolment, 8) annual admissions, 9) language of instruction, 10) duration of studies, 11) degrees obtainable, 12) number graduated annually, 13) tuition fees.

The many blank spaces in the tables indicate the difficulties inherent in compiling data primarily by the questionnaire method. Iron curtain information is particularly sketchy. In the Canadian and U. S. A. sections, the total enrolment figures appear to have been transposed into the annual admissions column.

The main value of this directory lies in the relative completeness of the list of schools and their admission requirements, degrees granted, and tuition fees. It is to be hoped that this edition will stimulate freer interchange of information, which will permit subsequent editions to be more complete.

E. M.

HUMAN BEHAVIOR IN THE CONCENTRATION CAMP. BY DR. ELIE A. COHEN. Pp. 295. New York: W. W. Norton & Co., 1953. Price, $5.00.

THIS is a book by a Dutch physician who was a prisoner at Auschwitz for 3 years during World War II. It describes in a systematic way the inhuman treatment accorded the inmates of concentration camps by Nazi physicians as well as by the jailers acting under the direction of the Nazi regime. The book describes the various means of extermination of human beings as well as the use of the prisoners for numerous experiments. It also deals with the disease encountered in concentration camps, the effects of hunger, the psychology of the prisoners and finally what the author believes to be the psychology of the SS. In his conclusions he is impressed with the capacity of the human being for endurance far beyond what is generally believed. He believes the educational philosophy of Germany had made the German mind unusually susceptible to Nazi theories.

Dr. Cohen was struck with the dominance and power of the hunger drive to overrule all other behavior. In conclusion he makes some interesting comments on what the change of environment and change of values in the concentration camp does to modify, often favorably, neuroses and psychosomatic disease. The need to cope with very real dangers reduced to nothingness many conflicts of "normal" life.

The author received a Doctor of Medical Science degree from the University of Utrecht in recognition of this book. It contains an extensive bibliography. O. E.

HUNTED HERETIC. THE LIFE AND DEATH OF MICHAEL SERVETUS 1511-1553. BY ROLAND H. BAINTON, Prof. of Ecclesiastical History at Yale. Pp. 270; 20 ills. Boston: Beacon Press, 1953. Price, $3.75.

SERVETUS was a true product of the Renaissance who included all knowledge in his survey: a subtle theologian, who spent years studying medicine at the University of Paris under Sylvius, Fernel and Gunther, and practicing it at Vienna, and a dabbler in geography and philology. It is not surprising, then, that he found nothing incongruous in describing a great discovery, the lesser or pulmonary circulation, in a few lines, incidentally as it were, in a book on the Restoration of Christianity. We of this modern period, however, are differently constituted, which may explain why the distinguished writer of the book under review is not convincing in the medical aspects of his presentation. In the 27 pages of the one chapter of medicine, Servetus' account of his discovery is given less than a page. A two-page analysis of the account brings out two important points: one, his denial of orifices in the ventricular septum, and second, his appreciation of the discrepancy between the size of the pulmonary artery and the amount of blood required to feed the lung (cp. Harvey's quantitative reasoning for the whole circulation). Priority of Servetus' observations over Columbo's is left as it must be, unsettled, and is dismissed by the author as of lessened importance in view of the much earlier discovery by Ibn An-Nafis (13th century).

On the non-medical aspects of Servetus' life and death, which very properly occupy

the greater part of the book, the reviewer is not competent to pass. Also like most medical men, he does not find the fine spun theological distinctions of four centuries ago either entertaining or profitable reading. This to be sure, does not apply to the same extent to non-medical readers, who might make the same point about some medico-historical works, and we may hope that the book will have a success. It seems to be well written and well documented, though one misses in the bibliography such works as Allwoerden (Latin and Dutch), Chéreau, Sigmund, and Wright. The author's style is clear and dignified. (We pass over the single exception noted (p. 118) where Luther is quoted "I got into the Pope's hair" as probably produced by some other translator.) Except for some crudely reproduced illustrations, which are not numbered, the book is satisfactorily produced and certainly would add to any library's Servetus section in helping fill the gap of an "adequate biography of the great sixteenth century heretic".

E. K.

ADRENAL CORTEX. TRANSACTIONS OF THE THIRD AND FOURTH CONFERENCES, NEW YORK CITY, 1951 AND 1952. Edited by ELAINE P. RALLI, M.D. 1951: Pp. 204, 58 ills. 1952: Pp. 165, 22 ills. New York: Josiah Macy, Jr. Foundation, 1952 and 1953. Price, $3.25 and $4.00 respectively.

THESE volumes are published by the Macy Foundation in an effort to share the very pertinent discussions of the conferences with physicians, investigators, teachers and students. The subjects included in the 1951 conference were: "Effects of Adrenal Cortical Hormones on Renal Function", "Hypothalamus and Regulation of ACTH Secretion", "Determination of Adrenal Cortical Steroids in Blood", "Biogenesis of Adrenal Cortical Steroids", and "Clinical Use of Adrenal Cortical Hormones and ACTH". The 1952 conference included: "Informal Discussion of Permissive Action of Adrenal Cortical Hormones", "Mechanisms Through Which the Adrenal Cortex Can Produce Qualitatively Different Effects", "Existence, Nature and Site of Production of a Salt Hormone (Mineralo-corticoid) Secreted by the Adrenal Gland", and "Adrenalectomy in Man". The great importance of adrenal cortex function in every field of medical practice, and the rapidity with which the frontier of knowledge in this field is being advanced constitute important reasons for study of these transcriptions by all physicians.

T. D.

LEIBESÜBUNGEN MIT KÖRPERBESCHÄDIGTEN, VOL. 2. By HANS LORENZEN. Pp. 249; 224 ills. Stuttgart: Georg Thieme Verlag, 1953. (Grune & Stratton, New York, U. S. Agents). Price, DM 22.50.

THIS is a second volume on this topic and a volume in a series entitled Work and Health edited by Drs. Bauer and Paetzold of the West German Ministry of Health. Lorenzen is an experienced teacher of athletics. He takes up the different types of athletic activities: games, running, jumping, throwing, gymnastics, bicycling, horseback riding, rowing, ice skating, skiing, fencing, bowling, dancing and hiking; and develops the possibilities for the physically handicapped: for the blind, deaf, mute, for those who have damage to the limbs including loss due to amputation.

It is properly pointed out how the exercises help to give the handicapped strength, joy and courage. There is a special chapter by H. Hoske, M.D., that stresses certain medical features of the problem with particular emphasis on the psychologic aspects of the physically handicapped. References are ample and there is a complete list available of teaching movies, both German and international. The illustrations are superb and teach more than could be accomplished by long description. The book is a symbol for the successful reconstruction of a nation that has gone through destruction in the past.

H. R.

SHOCK AND CIRCULATORY HOMEOSTASIS. Edited by HAROLD D. GREEN, M.D., Professor of Physiology and Pharmacology, Bowman Gray School of Medicine, Wake Forest College. Pp. 275; 57 ills. New York: Josiah Macy, Jr. Foundation, 1953. Price, $3.75.

THIS book consists of the Transactions of the Second Conference on Shock and Circulatory Homeostasis. As at the First Conference, the participants are outstanding authorities on the various phases of this subject. The first half is concerned with the metabolic effects of shock including hepatic and renal function and further discussion on the role of infection. The second half considers the physiologic functions of epinephrine and norepinephrine.

To those interested in research and the detailed physiologic changes in shock, this book is highly recommended. The average clinician, however, will experience difficulty in understanding and utilizing the majority of the information.

R. B.

HEART DISEASE. By PAUL DUDLEY WHITE, M.D., Executive Director, National Advisory Heart Council and Consultant to the Massachusetts General Hospital, Boston. 4th ed. Pp. 1015; 168 ills. New York: Macmillan Co., 1951. Price, $12.00.

THIS volume needs no introduction to the vast majority of physicians. The first edition in 1931 immediately achieved recognition as an outstanding Cardiology text, and the two intervening editions in 1937 and 1944 maintained this position of pre-eminence. The present volume has the same general arrangement as the others, the first part dealing with the Cardiovascular Examination, Symptoms and Signs; the second, with Prevalence, Causes and Types of Heart Disease; the third, with Structural Cardiovascular Abnormalities; and the fourth, with Disorders of Cardiovascular Function. Dr. White has done a remarkable job of keeping his book sufficiently small to be easy to handle, despite the need for including much new material. He has done this, furthermore, without any important deletions. This has been accomplished by abridging those sections dealing with certain diseases which are now very well-known and whose treatment has become routine, while at the same time amplifying the discussion of the more complicated types that are in the process of vigorous investigation. It is his opinion that, "as our knowledge of heart disease and particularly of its prevention develops during the next quarter century under the increasing program of research, we may hope that treatises on this subject in the future will become smaller and smaller as should current textbook chapters on typhoid fever and tuberculosis". This volume can be heartily recommended to all students and physicians desiring concise, authoritative knowledge of heart disease.

T. D.

ELECTROCARDIOGRAPHY IN PRACTICE. By ASHTON GRAYBIEL, M.D., PAUL D. WHITE, M.D., LOUISE WHEELER, A.M., AND CONGER WILLIAMS, M.D. 3rd ed. Pp. 376; 294 ills. Philadelphia: W. B. Saunders, 1952. Price, $10.00.

THERE are two types of electrocardiographic texts. The first presents the subject as a collection of facts and patterns which must be learned as a chore, and by brute memory. The second begins with the basic mechanisms involved and proceeds from these to the patterns which illustrate them. Both of these methods have had a place in medical education, but it is recognized now by most that the best way for a student to commence his learning is by the latter method. It will be far more pleasant (and even thrilling for many), and the effort required for eventual mastery will be far less. In fact, it is doubtful that anyone can ever truly master the subject by the former method alone. The place of the atlas of electrocardiography is, or should be, as a supplement to more basic texts.

The present volume is somewhat of a cross between the two methods. Its earlier chapters present considerable concise basic material, including a discussion of vectorcardiography. But then comes a hiatus and one finds that the remainder of the book is almost entirely a collection of pattern descriptions without any attempt at adequate explanation of mechanisms. The student must learn the "what" of bundle branch block, for example, without any understanding of the "how". He is not shown how and why the electrical position of the heart modifies the limb lead patterns seen with hypertrophy of the left ventricle, nor does he obtain any idea why Q-waves of certain types are found in some leads with particular types of myocardial infarction. He may have made a good start with the early chapters in acquiring basic knowledge, but the transition to the patterns is too abrupt for him and he may get the idea that the former has no practical bearing on the latter. Hence it seems to the reviewer that the book should attempt to remain either one or the other of the 2 types, but not to be parts of both.

Aside from this objection, however, the book is a fine one. An excellent collection of tracings is included, together with clinical data. The student of electrocardiography who has already become well founded in basic knowledge can profit by testing his acumen and locating his weak spots.

T. D.

THE PHYSIOPATHOLOGY OF CANCER. Edited By FREDDY HOMBURGER, M.D., AND WILLIAM H. FISHMAN, PH.D., Tufts College Medical School. Pp. 1031; 152 ills. New York: Paul B. Hoeber, 1953. Price, $18.00.

DURING the past two decades, research in the field of cancer has taken innumerable paths and channels of such diversity of direction that it has become virtually impossible for one mind to comprehend and keep abreast of what is going on. "The Physiopathology of Cancer" is, I presume, an attempt to correlate for those interested in cancer progress, a number of the disciplines

in cancer research. It is essentially a collection of treatises written by 28 different authors who have achieved eminence in one or another phase in this field. The list of contributors is impressive. The book is divided into four parts: Part I, Biology; Part II, Chemistry; Part III, Clinical Investigation; Part IV, Practical Applications.

It is obvious at the onset that no one could hope to achieve a complete correlation of the mountainous mass of heterogeneously related material on neoplasia between the covers of a single volume. Any such attempt must of necessity be merely an expression of the taste and reading experience of its authors or editors. Such is the quality and nature of this book. I seriously doubt that any one man capable of understanding all of its content could afford the time to read it through even though he would doubtless profit in so-doing.

This fact does not necessarily detract from the value of this treatise. Most of us interested in the new developments in the cancer field are vaguely aware of what is being done and where we can find an account of it. But the forces of a busy schedule and inertia prevent us from digging out the material which will enhance our knowledge. It is comforting to have "The Physiopathology of Cancer" at hand on our shelves. Its content is clearly indexed and if we happen to be curious about any of the topics treated therein we have but to turn to the proper section to satisfy our want.

This is distinctly a reference book and as such it will be of great help to a variety of workers in the medical field. If it fails to contain the specific information needed in a particular instance it is a reasonable and pardonable omission. The editors are to be congratulated upon the quality of the material they have collected. E. A.

NEW BOOKS

Symposium on Coal Miners' Pneumoconiosis. Held under the auspices of The Golden Clinic, Memorial General Hospital, Elkins, West Virginia. Pp. 95. Elkins, W. Va.: The Golden Clinic, Memorial General Hospital, 1953. Price, not given.

This is a verbatim transcript of an all-day symposium covering various aspects of Coal Miners' Pneumoconiosis. No tables or illustrations are included. Subjects discussed include: Clinical Aspects and Treatment, by Peter A. Theodos; X-ray and Gross Pathology by Louis L. Friedman; X-Ray Classification, Epidemiology, Pathology, and Pulmonary Function Studies by Philip Hughes (British Medical Research Council); and Lung Biopsy by Louis Mark.

Students of the subject will find interesting and valuable information in this brochure. R. C.

Ion Exchange Resins in Medicine and Biological Research. Edited by ROY WALDO MINER and HARRY SOBOTKA. New York: Annals of the New York Academy of Sciences, **57**, 61-324, 1953. Price, $4.50.

This monograph is a collection of papers presented at a conference on ion exchange resins in November, 1952, and sponsored by the New York Academy of Sciences. Each paper is concerned with a different aspect of ion exchangers, from synthesis and properties to applicability in chemistry, biology and medicine. In addition, a new process, termed ion exclusion, is described and the matter of ion exchange membranes is reviewed. There is no other single source of such diversified and authoritative considerations of ion exchange resins. J. Z.

Salt and the Heart. By EDWARD T. YORKE, M.D., Alexian Brothers Hospital. Pp. 83; 5 ills. Linden, N. J.: Drapkin, 1953. Price, $3.45.

This monograph purports to be a "fundamental discussion of the principles underlying the low sodium diet and the problem of salt accumulation within the body." Rather, it is a potpourri of truths, distortions and errors. It is not recommended to anyone. J. Z.

The Psychiatrist: His Training and Development. Edited by JOHN C. WHITEHORN, M.D., Chairman. Pp. 214. Washington: American Psychiatric Association, 1953. Price, not given.

This book is a report of the 1952 Conference on Psychiatric Education held at Cornell University, Ithaca, New York, June 19-25, 1952.

It is a comprehensive survey of psychiatric residency training. It covers the objectives, content, and methods of this specialty training, its historical development and growth, its many problems and basic concepts. Sections of the book are devoted to special fields, including administrative psychiatry, forensic psychiatry, industrial psychiatry, military psychiatry and psychiatry in civil defense, psychosomatic medicine, and child psychiatry.

Psychoanalysis and its role in general psychiatric training was fully discussed and summed up in the following statements:

1. It is not necessary to be psychoanalyzed in order to develop competence as a psychiatrist, including competence in psychotherapy and psychodynamics.
2. It is highly desirable that some persons should receive a personal psychoanalysis and psychoanalytic training because of the contributions which psychoanalysis may make in varying degrees to the personal adjustment of the psychiatrist, to his skills as a therapist, and to his understanding of the basic science of psychodynamics. For those who are to practice the specialty of psychoanalytic therapy, such psychoanalytic training is considered a necessity. Since the place of psychoanalysis in psychiatry has

been debated for some time by those both within and without the specialty, this conclusion will be of interest to many in medicine. O. E.

Managing Your Coronary. By WILLIAM A. BRAMS, M.D., Senior Attending Physician, Michael Reese Hospital, Chicago. Pp. 158; 18 ills. Philadelphia: J. B. Lippincott Co., 1953. Price, $2.95.

THE value of books written for patients has long been recognized in the treatment of diabetes mellitis, the results obtained often being proportional to the patient's understanding of his condition. Well written books on the subject have saved physicians hours that would be required otherwise for instruction of their patients.

In coronary disease, on the other hand, the problem of writing a book which will be of value to all patients is infinitely more complex. For some, greater knowledge of the intimate details of their disease is productive of greater anxiety; in others there is a need for some begetting of respect for the disease in order that orders will be obeyed. In his office the physician attempts to judge his patient and to govern his doses of reassurance or "laying down of the law" accordingly. It is impossible to write a book to meet all situations. For the in-between group, those that neither are overly anxious, or, on the other hand, those that do not require unusually firm tactics, a book of this type could be of real value. It is very well written, very instructive, and illustrated with picture drawings of do's and don't's. It should be noted, however, that the uncertain position taken with respect to diet is not likely to lead many patients to continue for long the limitations of a low fat diet. If such a diet is to be used a very firm stand on the part of the doctor is almost invariably necessary.

T. D.

NEW EDITIONS

Textbook of Physiology and Biochemistry. By GEORGE H. BELL, M.D., (University College), J. NORMAN DAVIDSON, M.D., (Glasgow), and HAROLD SCARBOROUGH, M.B., (Cardiff). 2nd ed. Pp. 961; illustrated. London: E. and S. Livingstone, Ltd., 1953. (Williams & Wilkins, Baltimore, U. S. Agents). Price, $10.00.

THE second edition of this excellent text has kept abreast of modern developments. The tried and proven basic material has been retained. As in the first edition this is a good way for medical students to study both Physiology and Biochemistry and at the same time become aware that their separation for didactic purposes is really artificial. The interrelation of these two important subjects is emphasized throughout the text.

M. O.

Handbook of Practical Bacteriology. A Guide to Bacteriological Laboratory Work. By T. J. MACKIE, Professor of Bacteriology, University of Edinburgh, and J. E. McCARTNEY, Medical Bacteriologist, Institute of Medical and Veterinary Science, Adelaide, South Australia. 9th ed. Pp. 667; many unnumbered illustrations and charts. Edinburgh and London: E. & S. Livingstone, Ltd. (Baltimore: Williams & Wilkins Co., U. S. Agents), 1953. Price, $5.50.

THE ninth edition of this popular and widely used text of practical bacteriology is a revision of the eighth edition published in 1948. In the latest edition, the format of the book remains essentially the same and in most instances the 24 chapter headings are identical or are little changed. Thus, about one-half of the text deals with general principles and methods and one-half with isolation and identification of specific micro-organisms and the character of diseases caused by these organisms.

Many recently published methods are included in the text such as: the Dubos medium for the tubercle bacillus; the Ludlam medium for *Staph. aureus;* the Elek and Christensen's media for Proteus; the Elek method for identifying toxigenic strains of *C. diphtheriae;* and others. Attention is also called to such new developments in the relationship of micro-organisms as that between Aerobacter and Klebsiella.

The text does not include a description of instrumentation for the measurements of pH and oxidation-reduction potentials and does not discuss adequately the importance of antibiotics such as aureomycin and chloramphenicol.

As in previous editions, however, the text includes many valuable methods and descriptive paragraphs which make it valuable for all workers in laboratory bacteriology. R. N.

Practical Methods in Biochemistry. By FREDERICK C. KOCH, Late Prof. Emeritus of Biochemistry, and MARTIN E. HANKE, Assoc. Prof. of Biochemistry, University of Chicago. 6th ed. Pp. 537; 28 ills. Baltimore: Williams & Wilkins Co., 1953. Price, $5.00.

THIS is a biochemistry laboratory manual designed for the use of medical students and graduate students in biochemistry. The new edition has been rearranged and new sections added. These include methods of isolation of cytochrome c and crystalline egg albumin; some new preparation methods for enzymes and experiments designed to illustrate the determination of Michaelis constants and enzyme-inhibitor rate constants. Methods are described for the determination of vitamins, hormones, and amino-acids by chemical and by microbiological methods. Paper chromatography is illustrated by the separation of amino-acids. An excellent section on the use of the manometric apparatus of Van Slyke and Neill is also included. Most of the colorimetric methods described refer only to the use of the visual colorimeter and if one desired to use the photoelectric instrument, as is recommended in the appendix, it would be necessary to modify some of the procedures outlined. The author has produced an excellent book for the medical and graduate student, as well as a book for reference. J. B.